PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C12N 15/31, 15/52, 15/82, 15/70, 5/10, 1/21, C12P 7/64, A01H 5/00

A1

(11) International Publication Number: WO 98/55625

(43) International Publication Date: 10 December 1998 (10.12.98)

(21) International Application Number: PCT/US98/11639

(22) International Filing Date: 4 June 1998 (04.06.98)

(30) Priority Data:
60/048,650 4 June 1997 (04.06.97) US

(71) Applicant: CALGENE, LLC [US/US]; 1920 Fifth Street, Davis, CA 95616 (US).

(72) Inventors: FACCIOTTI, Daniel; 2636 Lafayette Drive, Davis, CA 95616 (US). METZ, James, George; 2803 Belhaven Place, Davis, CA 95616 (US). LASSNER, Michael; 721 Falcon Avenue, Davis, CA 95616 (US).

(74) Agent: RAE-VENTER, Barbara; Rae-Venter Law Group, P.C., P.O. Box 60039, Palo Alto, CA 94306 (US).

(81) Designated States: BR, CA, IL, JP, MX, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PRODUCTION OF POLYUNSATURATED FATTY ACIDS BY EXPRESSION OF POLYKETIDE-LIKE SYNTHESIS GENES IN PLANTS

(57) Abstract

The present invention relates to compositions and methods for preparing polyunsaturated long chain fatty acids in plants, plant parts and plant cells, such as leaves, roots, fruits and seeds. Nucleic acid sequences and constructs encoding PKS-like genes required for the poly-unsaturated long chain fatty acid production, including the genes responsible for eicosapentenoic acid production of *Shewanella putrefaciens* and novel genes associated with the production of docosahexenoic acid in *Vibrio marinus* are used to generate transgenic plants, plant parts and cells which contain and express one or more transgenes encoding one or more of the PKS-like genes associated with such long chain polyunsaturated fatty acid production. Expression of the PKS-like genes in the plant system permits the large scale production of polyunsaturated long chain fatty acids such as eicosapentenoic acid and docosahexenoic acid for modification of the fatty acid profile of plants, plant parts and tissues. Manipulation of the fatty acid profiles allows for the production of commercial quantities of novel plant oils and products.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

PRODUCTION OF POLYUNSATURATED FATTY ACIDS BY EXPRESSION OF POLYKETIDE-LIKE SYNTHESIS GENES IN PLANTS

INTRODUCTION

Field of the Invention

This invention relates to modulating levels of enzymes and/or enzyme components capable of modifying long chain poly-unsaturated fatty acids (PUFAs) in a host cell, and constructs and methods for producing PUFAs in a host cell. The invention is exemplified by production of eicosapentenoic acid (EPA) using genes derived from *Shewanella putrefaciens* and *Vibrio marinus*.

Background

Two main families of poly-unsaturated fatty acids (PUFAs) are the ω3 fatty acids, exemplified by eicosapentenoic acid, and the ω6 fatty acids, exemplified by arachidonic acid. PUFAs are important components of the plasma membrane of the cell, where they can be found in such forms as phospholipids, and also can be found in triglycerides. PUFAs also serve as precursors to other molecules of importance in human beings and animals, including the prostacyclins, leukotrienes and prostaglandins. Long chain PUFAs of importance include docosahexenoic acid (DHA) and eicosapentenoic acid (EPA), which are found primarily in different types of fish oil, gamma-linolenic acid (GLA), which is found in the seeds of a number of plants, including evening primrose (*Oenothera biennis*), borage (*Borago officinalis*) and black currants (*Ribes nigrum*), stearidonic acid (SDA), which is found in marine oils and plant seeds, and arachidonic acid (ARA), which along with GLA is found in filamentous fungi. ARA can be purified from animal tissues including liver and adrenal gland. Several genera of marine bacteria are known which synthesize either EPA or DHA. DHA is present in human milk along with ARA.

PUFAs are necessary for proper development, particularly in the developing infant brain, and for tissue formation and repair. As an example, DHA, is an important constituent of many human cell membranes, in particular nervous cells (gray matter), muscle cells, and spermatozoa and believed to affect the development of brain functions in general and to be essential for the development of eyesight. EPA and DHA have a number of nutritional and pharmacological uses. As an example adults affected by diabetes (especially non insulin-dependent) show deficiencies and imbalances in their

levels of DHA which are believed to contribute to later coronary conditions. Therefore a diet balanced in DHA may be beneficial to diabetics.

For DHA, a number of sources exist for commercial production including a variety of marine organisms, oils obtained from cold water marine fish, and egg yolk fractions. The purification of DHA from fish sources is relatively expensive due to technical difficulties, making DHA expensive and in short supply. In algae such as *Amphidinium* and *Schyzochytrium* and marine fungi such as *Thraustochytrium* DHA may represent up to 48% of the fatty acid content of the cell. A few bacteria also are reported to produce DHA. These are generally deep sea bacteria such as *Vibrio marinus*. For ARA, microorganisms including the genera *Mortierella, Entomophthora, Phytium* and *Porphyridium* can be used for commercial production. Commercial sources of SDA include the genera *Trichodesma* and *Echium*. Commercial sources of GLA include evening primrose, black currants and borage. However, there are several disadvantages associated with commercial production of PUFAs from natural sources. Natural sources of PUFA, such as animals and plants, tend to have highly heterogeneous oil compositions. The oils obtained from these sources can require extensive purification to separate out one or more desired PUFA or to produce an oil which is enriched in one or more desired PUFA.

Natural sources also are subject to uncontrollable fluctuations in availability. Fish stocks may undergo natural variation or may be depleted by overfishing. Animal oils, and particularly fish oils, can accumulate environmental pollutants. Weather and disease can cause fluctuation in yields from both fish and plant sources. Cropland available for production of alternate oil-producing crops is subject to competition from the steady expansion of human populations and the associated increased need for food production on the remaining arable land. Crops which do produce PUFAs, such as borage, have not been adapted to commercial growth and may not perform well in monoculture. Growth of such crops is thus not economically competitive where more profitable and better established crops can be grown. Large -scale fermentation of organisms such as *Shewanella* also is expensive. Natural animal tissues contain low amounts of ARA and are difficult to process. Microorganisms such as *Porphyridium* and *Shewanella* are difficult to cultivate on a commercial scale.

Dietary supplements and pharmaceutical formulations containing PUFAs can retain the disadvantages of the PUFA source. Supplements such as fish oil capsules can

contain low levels of the particular desired component and thus require large dosages. High dosages result in ingestion of high levels of undesired components, including contaminants. Care must be taken in providing fatty acid supplements, as overaddition may result in suppression of endogenous biosynthetic pathways and lead to competition with other necessary fatty acids in various lipid fractions *in vivo*, leading to undesirable results. For example, Eskimos having a diet high in ω3 fatty acids have an increased tendency to bleed (U.S. Pat. No. 4,874,603). Fish oils have unpleasant tastes and odors, which may be impossible to economically separate from the desired product, such as a food supplements. Unpleasant tastes and odors of the supplements can make such regimens involving the supplement undesirable and may inhibit compliance by the patient.

A number of enzymes have been identified as being involved in PUFA biosynthesis. Linoleic acid (LA, 18:2 Δ 9, 12) is produced from oleic acid (18:1 Δ9) by a Δ12-desaturase. GLA (18:3 Δ 6, 9, 12) is produced from linoleic acid (LA, 18:2 Δ9, 12) by a Δ6-desaturase. ARA (20:4 Δ 5, 8, 11, 14) is produced from DGLA (20:3 Δ 8, 11, 14), catalyzed by a Δ5-desaturase. Eicosapentenoic acid (EPA) is a 20 carbon, omega 3 fatty acid containing 5 double bonds (Δ 5, 8, 11, 14, 17), all in the *cis* configuration. EPA, and the related DHA (Δ 4, 7, 10, 13, 16, 19, C22:6) are produced from oleic acid by a series of elongation and desaturation reactions. Additionally, an elongase (or elongases) is required to extend the 18 carbon PUFAs out to 20 and 22 carbon chain lengths. However, animals cannot convert oleic acid (18:1 Δ 9) into linoleic acid (18:2 Δ 9, 12). Likewise, μ-linolenic acid (ALA, 18:3 Δ 9, 12, 15) cannot be synthesized by mammals. Other eukaryotes, including fungi and plants, have enzymes which desaturate at positions Δ12 and Δ15. The major poly-unsaturated fatty acids of animals therefore are either derived from diet and/or from desaturation and elongation of linoleic acid (18:2 Δ 9, 12) or μ-linolenic acid (18:3 Δ 9, 12, 15).

Poly-unsaturated fatty acids are considered to be useful for nutritional, pharmaceutical, industrial, and other purposes. An expansive supply of poly-unsaturated fatty acids from natural sources and from chemical synthesis are not sufficient for commercial needs. Because a number of separate desaturase and elongase enzymes are required for fatty acid synthesis from linoleic acid (LA, 18:2 Δ 9, 12), common in most plant species, to the more saturated and longer chain PUFAs, engineering plant host cells for the expression of EPA and DHA may require expression of five or six separate

enzyme activities to achieve expression, at least for EPA and DHA, and for production of quantities of such PUFAs additional engineering efforts may be required, for instance the down regulation of enzymes competing for substrate, engineering of higher enzyme activities such as by mutagenesis or targeting of enzymes to plastid organelles. Therefore it is of interest to obtain genetic material involved in PUFA biosynthesis from species that naturally produce these fatty acids and to express the isolated material alone or in combination in a heterologous system which can be manipulated to allow production of commercial quantities of PUFAs.

Relevant Literature

Several genera of marine bacteria have been identified which synthesize either EPA or DHA (DeLong and Yayanos, *Applied and Environmental Microbiology* (1986) 51: 730-737). Researchers of the Sagami Chemical Research Institute have reported EPA production in *E. coli* which have been transformed with a gene cluster from the marine bacterium, *Shewanella putrefaciens*. A minimum of 5 open reading frames (ORFs) are required for fatty acid synthesis of EPA in *E. coli*. To date, extensive characterization of the functions of the proteins encoded by these genes has not been reported (Yazawa (1996) *Lipids* 31, S-297; WO 93/23545; WO 96/21735).

The protein sequence of open reading frame (ORF) 3 as published by Yazawa, USPN 5,683,898 is not a functional protein. Yazawa defines the protein as initiating at the methionine codon at nucleotides 9016-9014 of the *Shewanella* PKS-like cluster (Genbank accession U73935) and ending at the stop codon at nucleotides 8185-8183 of the *Shewanella* PKS-like cluster. However, when this ORF is expressed under control of a heterologous promoter in an *E. coli* strain containing the entire PKS-like cluster except ORF 3, the recombinant cells do not produce EPA.

Polyketides are secondary metabolites the synthesis of which involves a set of enzymatic reactions analogous to those of fatty acid synthesis (see reviews: Hopwood and Sherman, *Annu. Rev. Genet.* (1990) 24: 37-66, and Katz and Donadio, *in Annual Review of Microbiology* (1993) 47: 875-912). It has been proposed to use polyketide synthases to produce novel antibiotics (Hutchinson and Fujii, *Annual Review of Microbiology* (1995) 49:201-238).

SUMMARY OF THE INVENTION

Novel compositions and methods are provided for preparation of long chain poly-unsaturated fatty acids (PUFAs) using polyketide-like synthesis (PKS-like) genes in plants and plant cells. In contrast to the known and proposed methods for production of PUFAs by means of fatty acid synthesis genes, by the invention constructs and methods are provided for producing PUFAs by utilizing genes of a PKS-like system. The methods involve growing a host cell of interest transformed with an expression cassette functional in the host cell, the expression cassette comprising a transcriptional and translational initiation regulatory region, joined in reading frame 5' to a DNA sequence to a gene or component of a PKS-like system capable of modulating the production of PUFAs (PKS-like gene). An alteration in the PUFA profile of host cells is achieved by expression following introduction of a complete PKS-like system responsible for a PUFA biosynthesis into host cells. The invention finds use for example in the large scale production of DHA and EPA and for modification of the fatty acid profile of host cells and edible plant tissues and/or plant parts.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 provides designations for the ORFs of the EPA gene cluster of *Shewanella*. Figure 1A shows the organization of the genes; those ORFs essential for EPA production in *E. coli* are numbered. Figure 1B shows the designations given to subclones.

Figure 2 provides the *Shewanella* PKS-like domain structure, motifs and 'Blast' matches of ORF 6 (Figure 2A), ORF 7 (Figure 2B), ORF 8 (Figure 2C), ORF 9 (Figure 2D) and ORF 3 (Figure 2E). Figure 2F shows the structure of the region of the Anabeana chromosome that is related to domains present in *Shewanella* EPA ORFs.

Figure 3 shows results for pantethenylation - ORF 3 in *E. coli* strain SJ16.

Figure 4 is the sequence for the PKS-like cluster found in *Shewanella*, containing ORFs 3, 4, 5, 6, 7, 8 and 9. The start and last codons for each ORF are as follows: ORF3 (published-inactive): 9016, 8186; ORF3 (active in EPA synthesis): 9157, 8186; ORF 6: 13906, 22173; ORF 7: 22203, 24515; ORF 8: 24518, 30529; ORF 9: 30730, 32358.

Figure 5 shows the sequence for the PKS-like cluster in an approximately 40 kb DNA fragment of *Vibrio marinus*, containing ORFs 6, 7, 8 and 9. The start and last condons for each ORF are as follows: ORF 6: 17394, 25352; ORF 7: 25509, 28160; ORF 8: 28209, 34265; ORF 9: 34454, 36118.

Figure 6 shows the sequence for an approximately 19 kb portion of the PKS-like cluster of Figure 5 which contains the ORFs 6, 7, 8 and 9. The start and last condons for each ORF are as follows: ORF 6: 411, 8369; ORF 7: 8526, 11177; ORF 8: 11226, 17282; ORF 9: 17471, 19135.

Figure 7 shows a comparison of the PKS-like gene clusters of *Shewanella putrefaciens* and *Vibrio marinus*; Figure 7B is the *Vibrio marinus* operon sequence.

Figure 8 is an expanded view of the PKS-like gene cluster portion of *Vibrio marinus* shown in Figure 7B showing that ORFs 6, 7 and 8 are in reading frame 2, while ORF 9 is in reading frame 3.

Figure 9 demonstrates sequence homology of ORF 6 of *Shewanella putrefaciens* and *Vibrio marinus*. The *Shewanella* ORF 6 is depicted on the vertical axis, and the *Vibrio* ORF 6 is depicted on the horizontal axis. Lines indicate regions of the proteins that have a 60% identity. The repeated lines in the middle correspond to the multiple ACP domains found in ORF 6.

Figure 10 demonstrates sequence homology of ORF 7 of *Shewanella putrefaciens* and *Vibrio marinus*. The *Shewanella* ORF 7 is depicted on the vertical axis, and the *Vibrio* ORF 7 is depicted on the horizontal axis. Lines indicate regions of the proteins that have a 60% identity.

Figure 11 demonstrates sequence homology of ORF 8 of *Shewanella putrefaciens* and *Vibrio marinus*. The *Shewanella* ORF 8 is depicted on the vertical axis, and the *Vibro*. ORF 8 is depicted on the horizontal axis. Lines indicate regions of the proteins that have a 60% identity.

Figure 12 demonstrates sequence homology of ORF 9 of *Shewanella putrefaciens* and *Vibrio marinus*. The *Shewanella* ORF 9 is depicted on the vertical axis, and the *Vibrio* ORF 9 is depicted on the horizontal axis. Lines indicate regions of the proteins that have a 60% identity.

Figure 13 is a depiction of various complementation experiments, and resulting PUFA production. On the right, is shown the longest PUFA made in the *E. coli* strain

containing the *Vibrio* and *Shewanella* genes depicted on the left. The hollow boxes indicate ORFs from *Shewanella*. The solid boxes indicate ORFs from *Vibrio*.

Figure 14 is a chromatogram showing fatty acid production from complementation of pEPAD8 from *Shewanella* (deletion ORF 8) with ORF 8 from *Shewanella*, in *E. coli* Fad E-. The chromatogram presents an EPA (20:5) peak.

Figure 15 is a chromatogram showing fatty acid production from complementation of pEPAD8 from *Shewanella* (deletion ORF 8) with ORF 8 from *Vibrio marinus*, in *E. coli* Fad E-. The chromatograph presents EPA (20:5) and DHA (22:6) peaks.

Figure 16 is a table of PUFA values from the ORF 8 complementation experiment, the chromatogram of which is shown in Figure 15.

Figure 17 is a plasmid map showing the elements of pCGN7770.

Figure 18 is a plasmid map showing the elements of pCGN8535.

Figure 19 is a plasmid map showing the elements of pCGN8537.

Figure 20 is a plasmid map showing the elements of pCGN8525.

Figure 21 is a comparison of the *Shewanella* ORFs as defined by Yazawa and those disclosed in Figure 4. When a protein starting at the leucine (TTG) codon at nucleotides 9157-9155 and ending at the stop codon at nucleotides 8185-8183 is expressed under control of a heterologous promoter in an *E. coli* strain containing the entire PKS-like cluster except ORF 3, the recombinant cells do produce EPA. Thus, the published protein sequence is likely to be wrong, and the coding sequence for the protein may start at the TTG codon at nucleotides 9157-9155 or the TTG codon at nucleotides 9172-9170. This information is critical to the expression of a functional PKS-like cluster heterologous system.

Figure 22 is a plasmid map showing the elements of pCGN8560.

Figure 23 is plasmid map showing the elements of pCGN8556.

Figure 24 shows the translated DNA sequence upstream of the published ORF 3. The ATG start codon at position 9016 is the start codon for the protein described by Yazawa *et al* (1996) *supra*. The other arrows depict TTG or ATT codons that can also serve as start codons in bacteria. When ORF 3 is started from the published ATG codon at 9016, the protein is not functional in making EPA. When ORF 3 is initiated at the TTG codon at position 9157, the protein is capable of facilitating EPA synthesis.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In accordance with the subject invention, novel DNA sequences, DNA constructs and methods are provided, which include some or all of the polyketide-like synthesis (PKS-like) pathway genes from *Shewanella, Vibrio* or other microorganisms, for modifying the poly-unsaturated long chain fatty acid content of host cells, particularly host plant cells. The present invention demonstrates that EPA synthesis genes in *Shewanella putrefaciens* constitute a polyketide-like synthesis pathway. Functions are ascribed to the *Shewanella* and *Vibrio* genes and methods are provided for the production of EPA and DHA in host cells. The method includes the step of transforming cells with an expression cassette comprising a DNA encoding a polypeptide capable of increasing the amount of one or more PUFA in the host cell. Desirably, integration constructs are prepared which provide for integration of the expression cassette into the genome of a host cell. Host cells are manipulated to express a sense or antisense DNA encoding a polypeptide(s) that has PKS-like gene activity. By "PKS-like gene" is intended a polypeptide which is responsible for any one or more of the functions of a PKS-like activity of interest. By "polypeptide" is meant any chain of amino acids, regardless of length or post-translational modification, for example, glycosylation or phosphorylation. Depending upon the nature of the host cell, the substrate(s) for the expressed enzyme may be produced by the host cell or may be exogenously supplied. Of particular interest is the selective control of PUFA production in plant tissues and/or plant parts such as leaves, roots, fruits and seeds. The invention can be used to synthesize EPA, DHA, and other related PUFAs in host cells.

There are many advantages to transgenic production of PUFAs. As an example, in transgenic *E. coli* as in *Shewanella*, EPA accumulates in the phospholipid fraction, specifically in the *sn*-2 position. It may be possible to produce a structured lipid in a desired host cell which differs substantially from that produced in either *Shewanella* or *E. coli*. Additionally transgenic production of PUFAs in particular host cells offers several advantages over purification from natural sources such as fish or plants. In transgenic plants, by utilizing a PKS-like system, fatty acid synthesis of PUFAs is achieved in the cytoplasm by a system which produces the PUFAs through *de novo* production of the fatty acids utilizing malonyl Co-A and acetyl Co-A as substrates. In this fashion, potential problems, such as those associated with substrate competition and diversion of normal products of fatty acid synthesis in a host to PUFA production, are avoided.

Production of fatty acids from recombinant plants provides the ability to alter the naturally occurring plant fatty acid profile by providing new synthetic pathways in the host or by suppressing undesired pathways, thereby increasing levels of desired PUFAs, or conjugated forms thereof, and decreasing levels of undesired PUFAs. Production of fatty acids in transgenic plants also offers the advantage that expression of PKS-like genes in particular tissues and/or plant parts means that greatly increased levels of desired PUFAs in those tissues and/or parts can be achieved, making recovery from those tissues more economical. Expression in a plant tissue and/or plant part presents certain efficiencies, particularly where the tissue or part is one which is easily harvested, such as seed, leaves, fruits, flowers, roots, etc. For example, the desired PUFAs can be expressed in seed; methods of isolating seed oils are well established. In addition to providing a source for purification of desired PUFAs, seed oil components can be manipulated through expression of PKS-like genes, either alone or in combination with other genes such as elongases, to provide seed oils having a particular PUFA profile in concentrated form. The concentrated seed oils then can be added to animal milks and/or synthetic or semisynthetic milks to serve as infant formulas where human nursing is impossible or undesired, or in cases of malnourishment or disease in both adults and infants.

Transgenic microbial production of fatty acids offers the advantages that many microbes are known with greatly simplified oil compositions as compared with those of higher organisms, making purification of desired components easier. Microbial production is not subject to fluctuations caused by external variables such as weather and food supply. Microbially produced oil is substantially free of contamination by environmental pollutants. Additionally, microbes can provide PUFAs in particular forms which may have specific uses. For example, *Spirulina* can provide PUFAs predominantly at the first and third positions of triglycerides; digestion by pancreatic lipases preferentially releases fatty acids from these positions. Following human or animal ingestion of triglycerides derived from *Spirulina*, thes PUFAs are released by pancreatic lipases as free fatty acids and thus are directly available, for example, for infant brain development. Additionally, microbial oil production can be manipulated by controlling culture conditions, notably by providing particular substrates for microbially expressed enzymes, or by addition of compounds which suppress undesired biochemical pathways. In addition to these advantages, production of fatty acids from recombinant microbes provides the ability to alter the naturally occurring microbial fatty acid profile by

providing new synthetic pathways in the host or by suppressing undesired pathways, thereby increasing levels of desired PUFAs, or conjugated forms thereof, and decreasing levels of undesired PUFAs.

Production of fatty acids in animals also presents several advantages. Expression of desaturase genes in animals can produce greatly increased levels of desired PUFAs in animal tissues, making recovery from those tissues more economical. For example, where the desired PUFAs are expressed in the breast milk of animals, methods of isolating PUFAs from animal milk are well established. In addition to providing a source for purification of desired PUFAs, animal breast milk can be manipulated through expression of desaturase genes, either alone or in combination with other human genes, to provide animal milks with a PUFA composition substantially similar to human breast milk during the different stages of infant development. Humanized animal milks could serve as infant formulas where human nursing is impossible or undesired, or in the cases of malnourishment or disease.

DNAs encoding desired PKS-like genes can be identified in a variety of ways. In one method, a source of a desired PKS-like gene, for example genomic libraries from a *Shewanella* or *Vibrio* spp., is screened with detectable enzymatically- or chemically-synthesized probes. Sources of ORFs having PKS-like genes are those organisms which produce a desired PUFA, including DHA-producing or EPA-producing deep sea bacteria growing preferentially under high pressure or at relatively low temperature. Microorgansims such as *Shewanella* which produce EPA or DHA also can be used as a source of PKS-like genes. The probes can be made from DNA, RNA, or non-naturally occurring nucleotides, or mixtures thereof. Probes can be enzymatically synthesized from DNAs of known PKS-like genes for normal or reduced-stringency hybridization methods. For discussions of nucleic acid probe design and annealing conditions, see, for example, Sambrook *et al*, *Molecular Cloning: A Laboratory Manual* (2nd ed.), Vols. 1-3, *Cold Spring Harbor Laboratory*, (1989) or *Current Protocols in Molecular Biology*, F. Ausubel *et al*, ed., Greene Publishing and Wiley-Interscience, New York (1987), each of which is incorporated herein by reference. Techniques for manipulation of nucleic acids encoding PUFA enzymes such as subcloning nucleic acid sequences encoding polypeptides into expression vectors, labelling probes, DNA hybridization, and the like are described generally in Sambrook, *supra*.

Oligonucleotide probes also can be used to screen sources and can be based on sequences of known PKS-like genes, including sequences conserved among known PKS-like genes, or on peptide sequences obtained from a desired purified protein. Oligonucleotide probes based on amino acid sequences can be degenerate to encompass the degeneracy of the genetic code, or can be biased in favor of the preferred codons of the source organism. Alternatively, a desired protein can be entirely sequenced and total synthesis of a DNA encoding that polypeptide performed.

Once the desired DNA has been isolated, it can be sequenced by known methods. It is recognized in the art that such methods are subject to errors, such that multiple sequencing of the same region is routine and is still expected to lead to measurable rates of mistakes in the resulting deduced sequence, particularly in regions having repeated domains, extensive secondary structure, or unusual base compositions, such as regions with high GC base content. When discrepancies arise, resequencing can be done and can employ special methods. Special methods can include altering sequencing conditions by using: different temperatures; different enzymes; proteins which alter the ability of oligonucleotides to form higher order structures; altered nucleotides such as ITP or methylated dGTP; different gel compositions, for example adding formamide; different primers or primers located at different distances from the problem region; or different templates such as single stranded DNAs. Sequencing of mRNA can also be employed.

For the most part, some or all of the coding sequences for the polypeptides having PKS-like gene activity are from a natural source. In some situations, however, it is desirable to modify all or a portion of the codons, for example, to enhance expression, by employing host preferred codons. Host preferred codons can be determined from the codons of highest frequency in the proteins expressed in the largest amount in a particular host species of interest. Thus, the coding sequence for a polypeptide having PKS-like gene activity can be synthesized in whole or in part. All or portions of the DNA also can be synthesized to remove any destabilizing sequences or regions of secondary structure which would be present in the transcribed mRNA. All or portions of the DNA also can be synthesized to alter the base composition to one more preferable to the desired host cell. Methods for synthesizing sequences and bringing sequences together are well established in the literature. *In vitro* mutagenesis and selection, site-directed mutagenesis, or other means can be employed to obtain mutations of naturally occurring PKS-like genes to produce a polypeptide having PKS-like gene activity *in vivo* with more desirable

physical and kinetic parameters for function in the host cell, such as a longer half-life or a higher rate of production of a desired polyunsaturated fatty acid.

Of particular interest are the *Shewanella putrefaciens* ORFs and the corresponding ORFs of *Vibrio marinus*. The *Shewanella putrefaciens* PKS-like genes can be expressed in transgenic plants to effect biosynthesis of EPA. Other DNAs which are substantially identical in sequence to the *Shewanella putrefaciens* PKS-like genes, or which encode polypeptides which are substantially similar to PKS-like genes of *Shewanella putrefaciens* can be used, such as those identified from *Vibrio marinus*. By substantially identical in sequence is intended an amino acid sequence or nucleic acid sequence exhibiting in order of increasing preference at least 60%, 80%, 90% or 95% homology to the DNA sequence of the *Shewanella putrefaciens* PKS-like genes or nucleic acid sequences encoding the amino acid sequences for such genes. For polypeptides, the length of comparison sequences generally is at least 16 amino acids, preferably at least 20 amino acids, and most preferably 35 amino acids. For nucleic acids, the length of comparison sequences generally is at least 50 nucleotides, preferably at least 60 nucleotides, and more preferably at least 75 nucleotides, and most preferably, 110 nucleotides.

Homology typically is measured using sequence analysis software, for example, the Sequence Analysis software package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, Wisconsin 53705, MEGAlign (DNAStar, Inc., 1228 S. Park St., Madison, Wisconsin 53715), and MacVector (Oxford Molecular Group, 2105 S. Bascom Avenue, Suite 200, Campbell, California 95008). BLAST (National Center for Biotechnology Information (WCBI) www.ncbi.nlm.gov; FASTA (Pearson and Lipman, *Science* (1985) 227:1435-1446). Such software matches similar sequences by assigning degrees of homology to various substitutions, deletions, and other modifications. Conservative substitutions typically include substitutions within the following groups: glycine and alanine; valine, isoleucine and leucine; aspartic acid, glutamic acid, asparagine, and glutamine; serine and threonine; lysine and arginine; and phenylalanine and tyrosine. Substitutions may also be made on the basis of conserved hydrophobicity or hydrophilicity (Kyte and Doolittle, *J. Mol. Biol.* (1982) 157: 105-132), or on the basis of the ability to assume similar polypeptide secondary structure (Chou and Fasman, *Adv. Enzymol.* (1978) 47: 45-148, 1978). A

related protein to the probing sequence is identified when $p \geq 0.01$, preferably $p \geq 10^{-7}$ or 10^{-8}.

Encompassed by the present invention are related PKS-like genes from the same or other organisms. Such related PKS-like genes include variants of the disclosed PKS-like ORFs that occur naturally within the same or different species of *Shewanella*, as well as homologues of the disclosed PKS-like genes from other species and evolutionarily related proteins having analogous function and activity. Also included are PKS-like genes which, although not substantially identical to the *Shewanella putrefaciens* PKS-like genes, operate in a similar fashion to produce PUFAs as part of a PKS-like system. Related PKS-like genes can be identified by their ability to function substantially the same as the disclosed PKS-like genes; that is, they can be substituted for corresponding ORFs of *Shewanella* or *Vibrio* and still effectively produce EPA or DHA. Related PKS-like genes also can be identified by screening sequence databases for sequences homologous to the disclosed PKS-like genes, by hybridization of a probe based on the disclosed PKS-like genes to a library constructed from the source organism, or by RT-PCR using mRNA from the source organism and primers based on the disclosed PKS-like gene. Thus, the phrase "PKS-like genes" refers not only to the nucleotide sequences disclosed herein, but also to other nucleic acids that are allelic or species variants of these nucleotide sequences. It is also understood that these terms include nonnatural mutations introduced by deliberate mutation using recombinant technology such as single site mutation or by excising short sections of DNA open reading frames coding for PUFA enzymes or by substituting new codons or adding new codons. Such minor alterations substantially maintain the immunoidentity of the original expression product and/or its biological activity. The biological properties of the altered PUFA enzymes can be determined by expressing the enzymes in an appropriate cell line and by determining the ability of the enzymes to synthesize PUFAs. Particular enzyme modifications considered minor would include substitution of amino acids of similar chemical properties, e.g., glutamic acid for aspartic acid or glutamine for asparagine.

When utilizing a PUFA PKS-like system from another organism, the regions of a PKS-like gene polypeptide important for PKS-like gene activity can be determined through routine mutagenesis, expression of the resulting mutant polypeptides and determination of their activities. The coding region for the mutants can include deletions, insertions and point mutations, or combinations thereof. A typical functional analysis

begins with deletion mutagenesis to determine the N- and C-terminal limits of the protein necessary for function, and then internal deletions, insertions or point mutants are made in the open ready frame to further determine regions necessary for function. Other techniques such as cassette mutagenesis or total synthesis also can be used. Deletion mutagenesis is accomplished, for example, by using exonucleases to sequentially remove the 5' or 3' coding regions. Kits are available for such techniques. After deletion, the coding region is completed by ligating oligonucleotides containing start or stop codons to the deleted coding region after 5' or 3' deletion, respectively. Alternatively, oligonucleotides encoding start or stop codons are inserted into the coding region by a variety of methods including site-directed mutagenesis, mutagenic PCR or by ligation onto DNA digested at existing restriction sites. Internal deletions can similarly be made through a variety of methods including the use of existing restriction sites in the DNA, by use of mutagenic primers via site directed mutagenesis or mutagenic PCR. Insertions are made through methods such as linker-scanning mutagenesis, site-directed mutagenesis or mutagenic PCR. Point mutations are made through techniques such as site-directed mutagenesis or mutagenic PCR.

Chemical mutagenesis also can be used for identifying regions of a PKS-like gene polypeptide important for activity. A mutated construct is expressed, and the ability of the resulting altered protein to function as a PKS-like gene is assayed. Such structure-function analysis can determine which regions may be deleted, which regions tolerate insertions, and which point mutations allow the mutant protein to function in substantially the same way as the native PKS-like gene. All such mutant proteins and nucleotide sequences encoding them are within the scope of the present invention. EPA is produced in *Shewanella* as the product of a PKS-like system, such that the EPA genes encode components of this system. In *Vibrio*, DHA is produced by a similar system. The enzymes which synthesize these fatty acids are encoded by a cluster of genes which are distinct from the fatty acid synthesis genes encoding the enzymes involved in synthesis of the C16 and C18 fatty acids typically found in bacteria and in plants. As the *Shewanella* EPA genes represent a PKS-like gene cluster, EPA production is, at least to some extent, independent of the typical bacterial type II FAS system. Thus, production of EPA in the cytoplasm of plant cells can be achieved by expression of the PKS-like pathway genes in plant cells under the control of appropriate plant regulatory signals.

EPA production in *E. coli* transformed with the *Shewanella* EPA genes proceeds during anaerobic growth, indicating that O_2-dependent desaturase reactions are not involved. Analyses of the proteins encoded by the ORFs essential for EPA production reveals the presence of domain structures characteristic of PKS-like systems. Fig. 2A shows a summary of the domains, motifs, and also key homologies detected by "BLAST" data bank searches. Because EPA is different from many of the other substances produced by PKS-like pathways, i.e., it contains 5, *cis* double bonds, spaced at 3 carbon intervals along the molecule, a PKS-like system for synthesis of EPA is not expected.

Further, BLAST searches using the domains present in the *Shewanella* EPA ORFs reveal that several are related to proteins encoded by a PKS-like gene cluster found in Anabeana. The structure of that region of the Anabeana chromosome is shown in Fig. 2F. The Anabeana PKS-like genes have been linked to the synthesis of a long-chain (C26), hydroxy-fatty acid found in a glycolipid layer of heterocysts. The EPA protein domains with homology to the Anabeana proteins are indicated in Fig. 2F.

ORF 6 of *Shewanella* contains a KAS domain which includes an active site motif (DXAC*) as well as a "GFGG" motif which is present at the end of many Type II KAS proteins (see Fig. 2A). Extended motifs are present but not shown here. Next is a malonyl-CoA:ACP acyl transferase (AT) domain. Sequences near the active site motif (GHS*XG) suggest it transfers malonate rather than methylmalonate, i.e., it resembles the acetate-like ATs. Following a linker region, there is a cluster of 6 repeating domains, each ~100 amino acids in length, which are homologous to PKS-like ACP sequences. Each contains a pantetheine binding site motif (LGXDS*(L/I)). The presence of 6 such ACP domains has not been observed previously in fatty acid synthases (FAS) or PKS-like systems. Near the end of the protein is a region which shows homology to ß-keto-ACP reductases (KR). It contains a pyridine nucleotide binding site motif "GXGXX(G/A/P)".

The *Shewanella* ORF 8 begins with a KAS domain, including active site and ending motifs (Fig. 2C). The best match in the data banks is with the Anabeana HglD. There is also a domain which has sequence homology to the N- terminal one half of the Anabeana HglC. This region also shows weak homology to KAS proteins although it lacks the active site and ending motifs. It has the characteristics of the so-called chain length factors (CLF) of Type II PKS-like systems. ORF 8 appears to direct the production of EPA versus DHA by the PKS-like system. ORF 8 also has two domains with homology to ß-hydroxyacyl-ACP dehydrases (DH). The best match for both domains is

with *E. coli* FabA, a bi-functional enzyme which carries out both the dehydrase reaction and an isomerization (*trans* to *cis*) of the resulting double bond. The first DH domain contains both the active site histidine (H) and an adjacent cysteine (C) implicated in FabA catalysis. The second DH domain has the active site H but lacks the adjacent C (Fig. 2C). Blast searches with the second DH domain also show matches to FabZ, a second *E. coli* DH, which does not possess isomerase activity.

The N-terminal half of ORF 7 (Fig. 2B) has no significant matches in the data banks. The best match of the C-terminal half is with a C-terminal portion of the Anabeana HglC. This domain contains an acyl-transferase (AT) motif (GXSXG). Comparison of the extended active site sequences, based on the crystal structure of the *E. coli* malonyl-CoA:ACP AT, reveals that ORF 7 lacks two residues essential for exclusion of water from the active site (*E. coli* nomenclature; Q11 and R117). These data suggest that ORF 7 may function as a thioesterase.

ORF 9 (Fig. 2D) is homologous to an ORF of unknown function in the Anabeana Hgl cluster. It also exhibits a very weak homology to NIFA, a regulatory protein in nitrogen fixing bacteria. A regulatory role for the ORF 9 protein has not been excluded. ORF 3 (Fig. 2E) is homologous to the Anabeana HetI as well as EntD from *E. coli* and Sfp of *Bacillus*. Recently, a new enzyme family of phosphopantetheinyl transferases has been identified that includes HetI, EntD and Sfp (Lamblot RH, *et al.* (1996) A new enzyme superfamily - the phophopantetheinyl transferases. *Chemistry & Biology*, Vol 3, #11, 923-936). The data of Fig. 3 demonstrates that the presence of ORF 3 is required for addition of ß-alanine (i.e. pantetheine) to the ORF 6 protein. Thus, ORF 3 encodes the phosphopantetheinyl transferase specific for the ORF 6 ACP domains. (*See*, Haydock SF *et al.* (1995) Divergent sequence motifs correlated with the substrate specificity of (methyl)malonyl-CoA:acyl carrier protein transacylase domains in modular polyketide synthases, *FEBS Lett.*, 374, 246-248). Malonate is the source of the carbons utilized in the extension reactions of EPA synthesis. Additionally, malonyl-CoA rather than malonyl-ACP is the AT substrate, i.e., the AT region of ORF 6 uses malonyl Co-A.

Once the DNA sequences encoding the PKS-like genes of an organism responsible for PUFA production have been obtained, they are placed in a vector capable of replication in a host cell, or propagated *in vitro* by means of techniques such as PCR or long PCR. Replicating vectors can include plasmids, phage, viruses, cosmids and the like. Desirable vectors include those useful for mutagenesis of the gene of interest or for

expression of the gene of interest in host cells. A PUFA synthesis enzyme or a homologous protein can be expressed in a variety of recombinantly engineered cells. Numerous expression systems are available for expression of DNA encoding a PUFA enzyme. The expression of natural or synthetic nucleic acids encoding PUFA enzyme is typically achieved by operably linking the DNA to a promoter (which is either constitutive or inducible) within an expression vector. By expression vector is meant a DNA molecule, linear or circular, that comprises a segment encoding a PUFA enzyme, operably linked to additional segments that provide for its transcription. Such additional segments include promoter and terminator sequences. An expression vector also may include one or more origins of replication, one or more selectable markers, an enhancer, a polyadenylation signal, etc. Expression vectors generally are derived from plasmid or viral DNA, and can contain elements of both. The term "operably linked" indicates that the segments are arranged so that they function in concert for their intended purposes, for example, transcription initiates in the promoter and proceeds through the coding segment to the terminator. *See* Sambrook *et al*, *supra*.

The technique of long PCR has made *in vitro* propagation of large constructs possible, so that modifications to the gene of interest, such as mutagenesis or addition of expression signals, and propagation of the resulting constructs can occur entirely *in vitro* without the use of a replicating vector or a host cell. *In vitro* expression can be accomplished, for example, by placing the coding region for the desaturase polypeptide in an expression vector designed for *in vitro* use and adding rabbit reticulocyte lysate and cofactors; labeled amino acids can be incorporated if desired. Such *in vitro* expression vectors may provide some or all of the expression signals necessary in the system used. These methods are well known in the art and the components of the system are commercially available. The reaction mixture can then be assayed directly for PKS-like enzymes for example by determining their activity, or the synthesized enzyme can be purified and then assayed.

Expression in a host cell can be accomplished in a transient or stable fashion. Transient expression can occur from introduced constructs which contain expression signals functional in the host cell, but which constructs do not replicate and rarely integrate in the host cell, or where the host cell is not proliferating. Transient expression also can be accomplished by inducing the activity of a regulatable promoter operably linked to the gene of interest, although such inducible systems frequently exhibit a low

basal level of expression. Stable expression can be achieved by introduction of a nucleic acid construct that can integrate into the host genome or that autonomously replicates in the host cell. Stable expression of the gene of interest can be selected for through the use of a selectable marker located on or transfected with the expression construct, followed by selection for cells expressing the marker. When stable expression results from integration, integration of constructs can occur randomly within the host genome or can be targeted through the use of constructs containing regions of homology with the host genome sufficient to target recombination with the host locus. Where constructs are targeted to an endogenous locus, all or some of the transcriptional and translational regulatory regions can be provided by the endogenous locus. To achieve expression in a host cell, the transformed DNA is operably associated with transcriptional and translational initiation and termination regulatory regions that are functional in the host cell.

Transcriptional and translational initiation and termination regions are derived from a variety of nonexclusive sources, including the DNA to be expressed, genes known or suspected to be capable of expression in the desired system, expression vectors, chemical synthesis The termination region can be derived from the 3' region of the gene from which the initiation region was obtained or from a different gene. A large number of termination regions are known to and have been found to be satisfactory in a variety of hosts from the same and different genera and species. The termination region usually is selected more as a matter of convenience rather than because of any particular property. When expressing more than one PKS-like ORF in the same cell, appropriate regulatory regions and expression methods should be used. Introduced genes can be propagated in the host cell through use of replicating vectors or by integration into the host genome. Where two or more genes are expressed from separate replicating vectors, it is desirable that each vector has a different means of replication. Each introduced construct, whether integrated or not, should have a different means of selection and should lack homology to the other constructs to maintain stable expression and prevent reassortment of elements among constructs. Judicious choices of regulatory regions, selection means and method of propagation of the introduced construct can be experimentally determined so that all introduced genes are expressed at the necessary levels to provide for synthesis of the desired products.

A variety of procaryotic expression systems can be used to express PUFA enzyme. Expression vectors can be constructed which contain a promoter to direct transcription, a ribosome binding site, and a transcriptional terminator. Examples of regulatory regions suitable for this purpose in *E. coli* are the promoter and operator region of the *E. coli* tryptophan biosynthetic pathway as described by Yanofsky (1984) *J. Bacteriol.*, 158:1018-1024 and the leftward promoter of phage lambda (Pλ) as described by Herskowitz and Hagen, (1980) *Ann. Rev. Genet.*, 14:399-445. The inclusion of selection markers in DNA vectors transformed in *E.coli* is also useful. Examples of such markers include genes specifying resistance to ampicillin, tetracycline, or chloramphenicol. Vectors used for expressing foreign genes in bacterial hosts generally will contain a selectable marker, such as a gene for antibiotic resistance, and a promoter which functions in the host cell. Plasmids useful for transforming bacteria include pBR322 (Bolivar, *et al*, (1977) *Gene* 2:95-113), the pUC plasmids (Messing,(1983) *Meth. Enzymol.* 101:20-77, Vieira and Messing, (1982) *Gene* 19:259-268), pCQV2 (Queen, *ibid.*), and derivatives thereof. Plasmids may contain both viral and bacterial elements. Methods for the recovery of the proteins in biologically active form are discussed in U.S. Patent Nos. 4,966,963 and 4,999,422, which are incorporated herein by reference. See Sambrook, *et al* for a description of other prokaryotic expression systems.

For expression in eukaryotes, host cells for use in practicing the present invention include mammalian, avian, plant, insect, and fungal cells. As an example, for plants, the choice of a promoter will depend in part upon whether constitutive or inducible expression is desired and whether it is desirable to produce the PUFAs at a particular stage of plant development and/or in a particular tissue. Considerations for choosing a specific tissue and/or developmental stage for expression of the ORFs may depend on competing substrates or the ability of the host cell to tolerate expression of a particular PUFA. Expression can be targeted to a particular location within a host plant such as seed, leaves, fruits, flowers, and roots, by using specific regulatory sequences, such as those described in USPN 5,463,174, USPN 4,943,674, USPN 5,106,739, USPN 5,175,095, USPN 5,420,034, USPN 5,188,958, and USPN 5,589,379. Where the host cell is a yeast, transcription and translational regions functional in yeast cells are provided, particularly from the host species. The transcriptional initiation regulatory regions can be obtained, for example from genes in the glycolytic pathway, such as alcohol dehydrogenase, glyceraldehyde-3-phosphate dehydrogenase (GPD),

phosphoglucoisomerase, phosphoglycerate kinase, etc. or regulatable genes such as acid phosphatase, lactase, metallothionein, glucoamylase, etc. Any one of a number of regulatory sequences can be used in a particular situation, depending upon whether constitutive or induced transcription is desired, the particular efficiency of the promoter in conjunction with the open-reading frame of interest, the ability to join a strong promoter with a control region from a different promoter which allows for inducible transcription, ease of construction, and the like. Of particular interest are promoters which are activated in the presence of galactose. Galactose-inducible promoters (GAL1, GAL7, and GAL10) have been extensively utilized for high level and regulated expression of protein in yeast (Lue *et al,* (1987) *Mol. Cell. Biol.* 7:3446; Johnston, (1987) *Microbiol. Rev.* 51:458). Transcription from the GAL promoters is activated by the GAL4 protein, which binds to the promoter region and activates transcription when galactose is present. In the absence of galactose, the antagonist GAL80 binds to GAL4 and prevents GAL4 from activating transcription. Addition of galactose prevents GAL80 from inhibiting activation by GAL4. Preferably, the termination region is derived from a yeast gene, particularly *Saccharomyces, Schizosaccharomyces, Candida* or *Kluyveromyces*. The 3' regions of two mammalian genes, γ interferon and α2 interferon, are also known to function in yeast.

Nucleotide sequences surrounding the translational initiation codon ATG have been found to affect expression in yeast cells. If the desired polypeptide is poorly expressed in yeast, the nucleotide sequences of exogenous genes can be modified to include an efficient yeast translation initiation sequence to obtain optimal gene expression. For expression in *Saccharomyces*, this can be done by site-directed mutagenesis of an inefficiently expressed gene by fusing it in-frame to an endogenous *Saccharomyces* gene, preferably a highly expressed gene, such as the lactase gene.

As an alternative to expressing the PKS-like genes in the plant cell cytoplasm, is to target the enzymes to the chloroplast. One method to target proteins to the chloroplast entails use of leader peptides attached to the N-termini of the proteins. Commonly used leader peptides are derived from the small subunit of plant ribulose bis phosphate carboxylase. Leader sequences from other chloroplast proteins may also be used. Another method for targeting proteins to the chloroplast is to transform the chloroplast genome (Stable transformation of chloroplasts of *Chlamydomonas reinhardtii* (1 green alga) using bombardment of recipient cells with high-velocity tungsten microprojectiles coated with foreign DNA has been described. *See*, for example, Blowers *et al Plant Cell*

(1989) *1*:123-132 and Debuchy *et al EMBO J* (1989) *8*:2803-2809. The transformation technique, using tungsten microprojectiles, is described by Kline *et al*, *Nature* (London) (1987) *327*:70-73). The most common method of transforming chloroplasts involves using biolistic techniques, but other techniques developed for the purpose may also be used. (Methods for targeting foreign gene products into chloroplasts (Shrier *et al EMBO J.* (1985) *4*:25-32) or mitochnodria (Boutry *et al*, *supra*) have been described. *See* also Tomai *et al Gen. Biol. Chem.* (1988) *263*:15104-15109 and US Patent No. 4,940,835 for the use of transit peptides for translocating nuclear gene products into the chloroplast. Methods for directing the transport of proteins to the chloroplast are reviewed in Kenauf *TIBTECH* (1987) *5*:40-47.

For producing PUFAs in avian species and cells, gene transfer can be performed by introducing a nucleic acid sequence encoding a PUFA enzyme into the cells following procedures known in the art. If a transgenic animal is desired, pluripotent stem cells of embryos can be provided with a vector carrying a PUFA enzyme encoding transgene and developed into adult animal (USPN 5,162,215; Ono *et al.* (1996) *Comparative Biochemistry and Physiology A 113*(3):287-292; WO 9612793; WO 9606160). In most cases, the transgene is modified to express high levels of the PKS-like enzymes in order to increase production of PUFAs. The transgenes can be modified, for example, by providing transcriptional and/or translational regulatory regions that function in avian cells, such as promoters which direct expression in particular tissues and egg parts such as yolk. The gene regulatory regions can be obtained from a variety of sources, including chicken anemia or avian leukosis viruses or avian genes such as a chicken ovalbumin gene.

Production of PUFAs in insect cells can be conducted using baculovirus expression vectors harboring PKS-like transgenes. Baculovirus expression vectors are available from several commercial sources such as Clonetech. Methods for producing hybrid and transgenic strains of algae, such as marine algae, which contain and express a desaturase transgene also are provided. For example, transgenic marine algae can be prepared as described in USPN 5,426,040. As with the other expression systems described above, the timing, extent of expression and activity of the desaturase transgene can be regulated by fitting the polypeptide coding sequence with the appropriate transcriptional and translational regulatory regions selected for a particular use. Of particular interest are promoter regions which can be induced under preselected growth

conditions. For example, introduction of temperature sensitive and/or metabolite responsive mutations into the desaturase transgene coding sequences, its regulatory regions, and/or the genome of cells into which the transgene is introduced can be used for this purpose.

The transformed host cell is grown under appropriate conditions adapted for a desired end result. For host cells grown in culture, the conditions are typically optimized to produce the greatest or most economical yield of PUFAs, which relates to the selected desaturase activity. Media conditions which may be optimized include: carbon source, nitrogen source, addition of substrate, final concentration of added substrate, form of substrate added, aerobic or anaerobic growth, growth temperature, inducing agent, induction temperature, growth phase at induction, growth phase at harvest, pH, density, and maintenance of selection. Microorganisms such as yeast, for example, are preferably grown using selected media of interest, which include yeast peptone broth (YPD) and minimal media (contains amino acids, yeast nitrogen base, and ammonium sulfate, and lacks a component for selection, for example uracil). Desirably, substrates to be added are first dissolved in ethanol. Where necessary, expression of the polypeptide of interest may be induced, for example by including or adding galactose to induce expression from a GAL promoter.

When increased expression of the PKS-like gene polypeptide in a host cell which expresses PUFA from a PKS-like system is desired, several methods can be employed. Additional genes encoding the PKS-like gene polypeptide can be introduced into the host organism. Expression from the native PKS-like gene locus also can be increased through homologous recombination, for example by inserting a stronger promoter into the host genome to cause increased expression, by removing destabilizing sequences from either the mRNA or the encoded protein by deleting that information from the host genome, or by adding stabilizing sequences to the mRNA (*see* USPN 4,910,141 and USPN 5,500,365). Thus, the subject host will have at least have one copy of the expression construct and may have two or more, depending upon whether the gene is integrated into the genome, amplified, or is present on an extrachromosomal element having multiple copy numbers. Where the subject host is a yeast, four principal types of yeast plasmid vectors can be used: Yeast Integrating plasmids (YIps), Yeast Replicating plasmids (YRps), Yeast Centromere plasmids (YCps), and Yeast Episomal plasmids (YEps). YIps lack a yeast replication origin and must be propagated as integrated elements in the yeast

genome. YRps have a chromosomally derived autonomously replicating sequence and are propagated as medium copy number (20 to 40), autonomously replicating, unstably segregating plasmids. YCps have both a replication origin and a centromere sequence and propagate as low copy number (10-20), autonomously replicating, stably segregating plasmids. YEps have an origin of replication from the yeast 2μm plasmid and are propagated as high copy number, autonomously replicating, irregularly segregating plasmids. The presence of the plasmids in yeast can be ensured by maintaining selection for a marker on the plasmid. Of particular interest are the yeast vectors pYES2 (a YEp plasmid available from Invitrogen, confers uracil prototrophy and a GAL1 galactose-inducible promoter for expression), and pYX424 (a YEp plasmid having a constitutive TP1 promoter and conferring leucine prototrophy; (Alber and Kawasaki (1982). *J. Mol. & Appl. Genetics* 1: 419).

The choice of a host cell is influenced in part by the desired PUFA profile of the transgenic cell, and the native profile of the host cell. Even where the host cell expresses PKS-like gene activity for one PUFA, expression of PKS-like genes of another PKS-like system can provide for production of a novel PUFA not produced by the host cell. In particular instances where expression of PKS-like gene activity is coupled with expression of an ORF 8 PKS-like gene of an organism which produces a different PUFA, it can be desirable that the host cell naturally have, or be mutated to have, low PKS-like gene activity for ORF 8. As an example, for production of EPA, the DNA sequence used encodes the polypeptide having PKS-like gene activity of an organism which produces EPA, while for production of DHA, the DNA sequences used are those from an organism which produces DHA. For use in a host cell which already expresses PKS-like gene activity it can be necessary to utilize an expression cassette which provides for overexpression of the desired PKS-like genes alone or with a construct to downregulate the activity of an existing ORF of the existing PKS-like system, such as by antisense or co-suppression. Similarly, a combination of ORFs derived from separate organisms which produce the same or different PUFAs using PKS-like systems may be used. For instance, the ORF 8 of *Vibrio* directs the expression of DHA in a host cell, even when ORFs 3, 6, 7 and 9 are from *Shewanella*, which produce EPA when coupled to ORF 8 of *Shewanella*. Therefore, for production of eicosapentanoic acid (EPA), the expression cassettes used generally include one or more cassettes which include ORFs 3, 6, 7, 8 and 9 from a PUFA-producing organism such as the marine bacterium *Shewanella*

putrefaciens (for EPA production) or *Vibrio marinus* (for DHA production). ORF 8 can be used for induction of DHA production, and ORF 8 of *Vibrio* can be used in conjunction with ORFs 3, 6, 7 and 9 of *Shewanella* to produce DHA. The organization and numbering scheme of the ORFs identified in the *Shewanella* gene cluster are shown in Fig 1A. Maps of several subclones referred to in this study are shown in Fig 1B. For expression of a PKS-like gene polypeptide, transcriptional and translational initiation and termination regions functional in the host cell are operably linked to the DNA encoding the PKS-like gene polypeptide.

Constructs comprising the PKS-like ORFs of interest can be introduced into a host cell by any of a variety of standard techniques, depending in part upon the type of host cell. These techniques include transfection, infection, bolistic impact, electroporation, microinjection, scraping, or any other method which introduces the gene of interest into the host cell (*see* USPN 4,743,548, USPN 4,795,855, USPN 5,068,193, USPN 5,188,958, USPN 5,463,174, USPN 5,565,346 and USPN 5,565,347). Methods of transformation which are used include lithium acetate transformation (*Methods in Enzymology*, (1991) 194:186-187). For convenience, a host cell which has been manipulated by any method to take up a DNA sequence or construct will be referred to as "transformed" or "recombinant" herein. The subject host will have at least have one copy of the expression construct and may have two or more, depending upon whether the gene is integrated into the genome, amplified, or is present on an extrachromosomal element having multiple copy numbers.

For production of PUFAs, depending upon the host cell, the several polypeptides produced by pEPA, ORFs 3, 6, 7, 8 and 9, are introduced as individual expression constructs or can be combined into two or more cassettes which are introduced individually or co-transformed into a host cell. A standard transformation protocol is used. For plants, where less than all PKS-like genes required for PUFA synthesis have been inserted into a single plant, plants containing a complementing gene or genes can be crossed to obtain plants containing a full complement of PKS-like genes to synthesize a desired PUFA.

The PKS-like-mediated production of PUFAs can be performed in either prokaryotic or eukaryotic host cells. The cells can be cultured or formed as part or all of a host organism including an animal. Viruses and bacteriophage also can be used with appropriate cells in the production of PUFAs, particularly for gene transfer, cellular

targeting and selection. Any type of plant cell can be used for host cells, including dicotyledonous plants, monocotyledonous plants, and cereals. Of particular interest are crop plants such as *Brassica*, *Arabidopsis*, soybean, corn, and the like. Prokaryotic cells of interest include *Eschericia, Baccillus, Lactobaccillus, cyanobacteria* and the like. Eukaryotic cells include plant cells, mammalian cells such as those of lactating animals, avian cells such as of chickens, and other cells amenable to genetic manipulation including insect, fungal, and algae cells. Examples of host animals include mice, rats, rabbits, chickens, quail, turkeys, cattle, sheep, pigs, goats, yaks, etc., which are amenable to genetic manipulation and cloning for rapid expansion of a transgene expressing population. For animals, PKS-like transgenes can be adapted for expression in target organelles, tissues and body fluids through modification of the gene regulatory regions. Of particular interest is the production of PUFAs in the breast milk of the host animal.

Examples of host microorganisms include *Saccharomyces cerevisiae*, *Saccharomyces carlsbergensis*, or other yeast such as *Candida, Kluyveromyces* or other fungi, for example, filamentous fungi such as *Aspergillus, Neurospora, Penicillium*, etc. Desirable characteristics of a host microorganism are, for example, that it is genetically well characterized, can be used for high level expression of the product using ultra-high density fermentation, and is on the GRAS (generally recognized as safe) list since the proposed end product is intended for ingestion by humans. Of particular interest is use of a yeast, more particularly baker's yeast (*S. cerevisiae*), as a cell host in the subject invention. Strains of particular interest are SC334 (Mat α pep4-3 prbl-1122 ura3-52 leu2-3, 112 regl-501 gal1; (Hovland *et al* (1989) Gene 83:57-64); BJ1995 (Yeast Genetic Stock Centre, 1021 Donner Laboratory, Berkeley, CA 94720), INVSC1 (Mat α hiw3Δ1 leu2 trp1-289 ura3-52 (Invitrogen, 1600 Faraday Ave., Carlsbad, CA 92008) and INVSC2 (Mat α his3Δ200 ura3-167; (Invitrogen). Bacterial cells also may be used as hosts. This includes *E. coli*, which can be useful in fermentation processes. Alternatively, a host such as a *Lactobacillus* species can be used as a host for introducing the products of the PKS-like pathway into a product such as yogurt.

The transformed host cell can be identified by selection for a marker contained on the introduced construct. Alternatively, a separate marker construct can be introduced with the desired construct, as many transformation techniques introduce multiple DNA molecules into host cells. Typically, transformed hosts are selected for their ability to grow on selective media. Selective media can incorporate an antibiotic or lack a factor

necessary for growth of the untransformed host, such as a nutrient or growth factor. An introduced marker gene therefor may confer antibiotic resistance, or encode an essential growth factor or enzyme, and permit growth on selective media when expressed in the transformed host cell. Desirably, resistance to kanamycin and the amino glycoside G418 are of particular interest (*see* USPN 5,034,322). For yeast transformants, any marker that functions in yeast can be used, such as the ability to grow on media lacking uracil, lencine, lysine or tryptophan.

Selection of a transformed host also can occur when the expressed marker protein can be detected, either directly or indirectly. The marker protein can be expressed alone or as a fusion to another protein. The marker protein can be one which is detected by its enzymatic activity; for example ß-galactosidase can convert the substrate X-gal to a colored product, and luciferase can convert luciferin to a light-emitting product. The marker protein can be one which is detected by its light-producing or modifying characteristics; for example, the green fluorescent protein of *Aequorea victoria* fluoresces when illuminated with blue light. Antibodies can be used to detect the marker protein or a molecular tag on, for example, a protein of interest. Cells expressing the marker protein or tag can be selected, for example, visually, or by techniques such as FACS or panning using antibodies.

The PUFAs produced using the subject methods and compositions are found in the host plant tissue and/or plant part as free fatty acids and/or in conjugated forms such as acylglycerols, phospholipids, sulfolipids or glycolipids, and can be extracted from the host cell through a variety of means well-known in the art. Such means include extraction with organic solvents, sonication, supercritical fluid extraction using for example carbon dioxide, and physical means such as presses, or combinations thereof. Of particular interest is extraction with methanol and chloroform. Where appropriate, the aqueous layer can be acidified to protonate negatively charged moieties and thereby increase partitioning of desired products into the organic layer. After extraction, the organic solvents can be removed by evaporation under a stream of nitrogen. When isolated in conjugated forms, the products are enzymatically or chemically cleaved to release the free fatty acid or a less complex conjugate of interest, and are then subjected to further manipulations to produce a desired end product. Desirably, conjugated forms of fatty acids are cleaved with potassium hydroxide.

If further purification is necessary, standard methods can be employed. Such methods include extraction, treatment with urea, fractional crystallization, HPLC, fractional distillation, silica gel chromatography, high speed centrifugation or distillation, or combinations of these techniques. Protection of reactive groups, such as the acid or alkenyl groups, can be done at any step through known techniques, for example alkylation or iodination. Methods used include methylation of the fatty acids to produce methyl esters. Similarly, protecting groups can be removed at any step. Desirably, purification of fractions containing DHA and EPA is accomplished by treatment with urea and/or fractional distillation.

The uses of the subject invention are several. Probes based on the DNAs of the present invention find use in methods for isolating related molecules or in methods to detect organisms expressing PKS-like genes. When used as probes, the DNAs or oligonucleotides need to be detectable. This is usually accomplished by attaching a label either at an internal site, for example via incorporation of a modified residue, or at the 5' or 3' terminus. Such labels can be directly detectable, can bind to a secondary molecule that is detectably labeled, or can bind to an unlabelled secondary molecule and a detectably labeled tertiary molecule; this process can be extended as long as is practicable to achieve a satisfactorily detectable signal without unacceptable levels of background signal. Secondary, tertiary, or bridging systems can include use of antibodies directed against any other molecule, including labels or other antibodies, or can involve any molecules which bind to each other, for example a biotin-streptavidin/avidin system. Detectable labels typically include radioactive isotopes, molecules which chemically or enzymatically produce or alter light, enzymes which produce detectable reaction products, magnetic molecules, fluorescent molecules or molecules whose fluorescence or light-emitting characteristics change upon binding. Examples of labelling methods can be found in USPN 5,011,770. Alternatively, the binding of target molecules can be directly detected by measuring the change in heat of solution on binding of a probe to a target via isothermal titration calorimetry, or by coating the probe or target on a surface and detecting the change in scattering of light from the surface produced by binding of a target or a probe, respectively, is done with the BIAcore system.

PUFAs produced by recombinant means find applications in a wide variety of areas. Supplementation of humans or animals with PUFAs in various forms can result in increased levels not only of the added PUFAs, but of their metabolic progeny as well.

Complex regulatory mechanisms can make it desirable to combine various PUFAs, or to add different conjugates of PUFAs, in order to prevent, control or overcome such mechanisms to achieve the desired levels of specific PUFAs in an individual. In the present case, expression of PKS-like gene genes, or antisense PKS-like gene transcripts, can alter the levels of specific PUFAs, or derivatives thereof, found in plant parts and/or plant tissues. The PKS-like gene polypeptide coding region is expressed either by itself or with other genes, in order to produce tissues and/or plant parts containing higher proportions of desired PUFAs or containing a PUFA composition which more closely resembles that of human breast milk (Prieto *et al.*, PCT publication WO 95/24494) than does the unmodified tissues and/or plant parts.

PUFAs, or derivatives thereof, made by the disclosed method can be used as dietary supplements for patients undergoing intravenous feeding or for preventing or treating malnutrition. For dietary supplementation, the purified PUFAs, or derivatives thereof, can be incorporated into cooking oils, fats or margarines formulated so that in normal use the recipient receives a desired amount of PUFA. The PUFAs also can be incorporated into infant formulas, nutritional supplements or other food products, and find use as anti-inflammatory or cholesterol lowering agents.

Particular fatty acids such as EPA can be used to alter the composition of infant formulas to better replicate the PUFA composition of human breast milk. The predominant triglyceride in human milk is reported to be 1,3-di-oleoyl-2-palmitoyl, with 2-palmitoyl glycerides reported as better absorbed than 2-oleoyl or 2-lineoyl glycerides (*see* USPN 4,876,107). Typically, human breast milk has a fatty acid profile comprising from about 0.15 % to about 0.36 % as DHA, from about 0.03 % to about 0.13 % as EPA, from about 0.30 % to about 0.88 % as ARA, from about 0.22 % to about 0.67 % as DGLA, and from about 0.27 % to about 1.04 % as GLA. A preferred ratio of GLA:DGLA:ARA in infant formulas is from about 1:1:4 to about 1:1:1, respectively. Amounts of oils providing these ratios of PUFA can be determined without undue experimentation by one of skill in the art. PUFAs, or host cells containing them, also can be used as animal food supplements to alter an animal's tissue or milk fatty acid composition to one more desirable for human or animal consumption.

For pharmaceutical use (human or veterinary), the compositions generally are administered orally but can be administered by any route by which they may be successfully absorbed, e.g., parenterally (i.e. subcutaneously, intramuscularly or

intravenously), rectally or vaginally or topically, for example, as a skin ointment or lotion. Where available, gelatin capsules are the preferred form of oral administration. Dietary supplementation as set forth above also can provide an oral route of administration. The unsaturated acids of the present invention can be administered in conjugated forms, or as salts, esters, amides or prodrugs of the fatty acids. Any pharmaceutically acceptable salt is encompassed by the present invention; especially preferred are the sodium, potassium or lithium salts. Also encompassed are the N-alkylpolyhydroxamine salts, such as N-methyl glucamine, described in PCT publication WO 96/33155. Preferred esters are the ethyl esters.

The PUFAs of the present invention can be administered alone or in combination with a pharmaceutically acceptable carrier or excipient. As solid salts, the PUFAs can also be administered in tablet form. For intravenous administration, the PUFAs or derivatives thereof can be incorporated into commercial formulations such as Intralipids. Where desired, the individual components of formulations can be individually provided in kit form, for single or multiple use. A typical dosage of a particular fatty acid is from 0.1 mg to 20 g, or even 100 g daily, and is preferably from 10 mg to 1, 2, 5 or 10 g daily as required, or molar equivalent amounts of derivative forms thereof. Parenteral nutrition compositions comprising from about 2 to about 30 weight percent fatty acids calculated as triglycerides are encompassed by the present invention. Other vitamins, and particularly fat-soluble vitamins such as vitamin A, D, E and L-carnitine optionally can be included. Where desired, a preservative such as a tocopherol can be added, typically at about 0.1% by weight.

The following examples are presented by way of illustration, not of limitation.

EXAMPLES

Example 1

The Identity of ORFs Derived from *Vibrio marinus*

Using polymerase chain reaction (PCR) with primers based on ORF 6 of *Shewanella* (Sp ORF 6) sequences (FW 5' primers CUACUACUACUACCAAGCT AAAGCACTTAACCGTG, and CUACUACUACUAACAGCGAAATGCTTATCAAG for *Vibrio* and SS9 respectively and 3' BW primers: CAUCAUCAUCAUGCGACC

AAAACCAAATGAGCTAATAC for both *Vibrio* and SS9) and genomic DNAs templates from *Vibrio* and a borophyllic *photobacter* producing EPA (provided by Dr. Bartlett, UC San Diego), resulted in PCR products of *ca.*400 bases for *Vibrio marinus* (*Vibrio*) and *ca.*900 bases for SS9 presenting more than 75% homology with corresponding fragments of Sp ORF 6 (*see* Figure 25) as determined by direct counting of homologous amino acids.

A *Vibrio* cosmid library was then prepared and using the *Vibrio* ORF 6 PCR product as a probe (*see* Figure 26); clones containing at least ORF 6 were selected by colony hybridization.

Through additional sequences of the selected cosmids such as cosmid #9 and cosmid #21, a *Vibrio* cluster (Figure 5) with ORFs homologous to, and organized in the same sequential order (ORFs 6-9) as ORFs 6-9 of *Shewanella*, was obtained (Figure 7). The *Vibrio* ORFs from this sequence are found at 17394 to 36115 and comprehend ORFs 6-9.

Table

Vibrio operon figures

17394	to 25349	length = 7956 nt
25509	to 28157	length = 2649 nt
28209	to 34262	length = 6054 nt
34454	to 36115	length = 1662 nt

The ORF designations for the *Shewanella* genes are based on those disclosed in Figure 4, and differ from those published for the *Shewanella* cluster (Yazawa *et al*, USPN 5,683,898). For instance, ORF 3 of Figure 4 is read in the opposite direction from the other ORFs and is not disclosed in Yazawa *et al* USPN 5,683,898 (See Fig. 24) for comparison with Yazawa *et al* USPN 5,683,898).

Sequences homologous to ORF 3, were not found in the proximity of ORF 6 (17000 bases upstream of ORF 6) or of ORF 9 (*ca.*4000 bases downstream of ORF 9). Motifs characteristic of phosphopantethenyl transferases (Lambalot *et al* (1996) *Current Biology* 3:923-936) were absent from the *Vibrio* sequences screened for these motifs. In addition, there was no match to Sp ORF 3 derived probes in genomic digests of *Vibrio* and of SC2A *Shewanella* (another bacterium provided by the University of San Diego and

also capable of producing EPA). Although ORF 3 may exist in *Vibrio*, its DNA may not be homologous to that of Sp ORF 3 and/or could be located in portions of the genome that were not sequenced.

Figure 6 provides the sequence of an approximately 19 kb *Vibrio* clone comprising ORFs 6-9. Figures 7 and 8 compare the gene cluster organizations of the PKS-like systems of *Vibrio marinus* and *Shewanella putrefacians*. Figures 9 through 12 show the levels of sequence homology between the corresponding ORFs 6, 7, 8 and 9, respectively.

Example 2

ORF 8 Directs DHA Production

As described in example 1, DNA homologous to *Sp* ORF 6 was found in an unrelated species, SS9 *Photobacter*, which also is capable of producing EPA. Additionally, ORFs homologous to *Sp* ORF 6-9 were found in the DHA producing V*brio marinus* (*Vibrio*). From these ORFs a series of experiments was designed in which deletions in each of *Sp* ORFs 6-9 that suppressed EPA synthesis in *E. coli* (Yazawa (1996) *supra*) were complemented by the corresponding homologous genes from *Vibrio*.

The *Sp* EPA cluster was used to determine if any of the *Vibrio* ORFs 6-9 was responsible for the production of DHA. Deletion mutants provided for each of the *Sp* ORFs are EPA and DHA null. Each deletion was then complemented by the corresponding *Vibrio* ORF expressed behind a *lac* promoter (Figure 13).

The complementation of a *Sp* ORF 6 deletion by a *Vibrio* ORF 6 reestablished the production of EPA. Similar results were obtained by complementing the *Sp* ORF 7 and ORF 9 deletions. By contrast, the complementation of a *Sp* ORF 8 deletion resulted in the production of C22:6. *Vibrio* ORF 8 therefore appears to be a key element in the synthesis of DHA. Figures 14 and 15 show chromatograms of fatty acid profiles from the respective complementations of Sp del ORF 6 with *Vibrio* ORF 6 (EPA and no DHA) and *Sp* del ORF 8 with *Vibrio* ORF 8 (DHA). Figure 16 shows the fatty acid percentages for the ORF 8 complementation, again demonstrating that ORF 8 is responsible for DHA production.

These data show that polyketide-like synthesis genes with related or similar ORFs can be combined and expressed in a heterologous system and used to produce a distinct PUFA species in the host system, and that ORF 8 has a role in determining the ultimate chain length. The *Vibrio* ORFs 6, 7, 8, and 9 reestablish EPA synthesis. In the case of

Vibrio ORF 8, DHA is also present (*ca.* 0.7%) along with EPA (*ca.* 0.6%) indicating that this gene plays a significant role in directing synthesis of DHA *vs* EPA for these systems.

Example 3

Requirements for Production of DHA

To determine how *Vibrio* ORFs of the cluster ORF 6-9 are used in combination with *Vibrio* ORF 8, some combinations of *Vibrio* ORF 8 with some or all of the other *Vibrio* ORFS 6-9 cluster were created to explain the synthesis of DHA.

Vibrio ORFs 6-9 were complemented with *Sp* ORF 3. The results of this complementation are presented in Figures 16b and 16c. The significant amounts of DHA measured (greater than about 9%) and the absence of EPA suggest that no ORFs other than those of *Vibrio* ORFs 6-9 are required for DHA synthesis when combined with *Sp* ORF 3. This suggests that *Sp* ORF 3 plays a general function in the synthesis of bacterial PUFAs.

With respect to the DHA vs EPA production, it may be necessary to combine *Vibrio* ORF 8 with other *Vibrio* ORFs of the 6-9 cluster in order to specifically produce DHA. The roles of *Vibrio* ORF 9 and each of the combinations of *Vibrio* ORFs (6,8), (7, 8), (8, 9), etc in the synthesis of DHA are being studied.

Example 4

Plant Expression Constructs

A cloning vector with very few restriction sites was designed to facilitate the cloning of large fragments and their subsequent manipulation. An adapter was assembled by annealing oligonucleotides with the sequences AAGCCCGGGCTT and GTACAAGCCCGGGCTTAGCT. This adapter was ligated to the vector pBluescript II SK+ (Stratagene) after digestion of the vector with the restriction endonucleases *Asp*718 and *Sst*I. The resulting vector, pCGN7769 had a single *Srf*I (and embedded *Sma*I) cloning site for the cloning of blunt ended DNA fragments.

A plasmid containing the napin cassette from pCGN3223, (USPN 5,639,790) was modified to make it more useful for cloning large DNA fragments containing multiple restriction sites, and to allow the cloning of multiple napin fusion genes into plant binary transformation vectors. An adapter comprised of the self annealed oligonucleotide of sequence CGCGATTTAAATGGCGCGCCCTGCAGGCGGCCGCCTGCAGGGCGC

GCCATTTAAAT was ligated into the vector pBC SK+ (Stratagene) after digestion of the vector with the restriction endonuclease *Bss*HII to construct vector pCGN7765. Plamids pCGN3223 and pCGN7765 were digested with *Not*I and ligated together. The resultant vector, pCGN7770 (Figure 17), contains the pCGN7765 backbone and the napin seed specific expression cassette from pCGN3223.

Shewanella constructs

Genes encoding the *Shewanella* proteins were mutagenized to introduce suitable cloning sites 5' and 3' ORFs using PCR. The template for the PCR reactions was DNA of the cosmid pEPA (Yazawa *et al, supra)*. PCR reactions were performed using Pfu DNA polymerase according to the manufacturers' protocols. The PCR products were cloned into *Srf*I digested pCGN7769. The primers CTGCAGCTCGAGACAATGTTGATT TCCTTATACTTCTGTCC and GGATCCAGATCTCTAGCTAGTCTTAGCTGAAGC TCGA were used to amplify ORF 3, and to generate plasmid pCGN8520. The primers TCTAGACTCGAGACAATGAGCCAGACCTCTAAACCTACA and CCCGGGCTC GAGCTAATTCGCCTCACTGTCGTTTGCT were used to amplify ORF 6, and generate plasmid pCGN7776. The primers GAATTCCTCGAGACAATGCCGCTGCGCATCG CACTTATC and GGTACCAGATCTTTAGACTTCCCCTTGAAGTAAATGG were used to amplify ORF 7, and generate plasmid pCGN7771. The primers GAATTCGTCG ACACAATGTCATTACCAGACAATGCTTCT and TCTAGAGTCGACTTATAC AGATTCTTCGATGCTGATAG were used to amplify ORF 8, and generate plasmid pCGN7775. The primers GAATTCGTCGACACAATGAATCCTACAGCAA CTAACGAA and TCTAGAGGATCCTTAGGCCATTCTTTGGTTTGGCTTC were used to amplify ORF 9, and generate plasmid pCGN7773.

The integrity of the PCR products was verified by DNA sequencing of the inserts of pCGN7771, PCGN8520, and pCGN7773. ORF 6 and ORF 8 were quite large in size. In order to avoid sequencing the entire clones, the center portions of the ORFs were replaced with restriction fragments of pEPA. The 6.6 kilobase *Pac*I/*Bam*HI fragment of pEPA containing the central portion of ORF 6 was ligated into *Pac*I/*Bam*HI digested pCGN7776 to yield pCGN7776B4. The 4.4 kilobase *Bam*HI/*Bgl*II fragment of pEPA containing the central portion of ORF 8 was ligated into *Bam*HI/*Bgl*II digested pCGN7775 to yield pCGN7775A. The regions flanking the pEPA fragment and the cloning junctions were verified by DNA sequencing.

Plasmid pCGN7771 was cut with *Xho*I and *Bgl*II and ligated to pCGN7770 after digestion with *Sal*I and BglII. The resultant napin/ORF 7 gene fusion plasmid was designated pCGN7783. Plasmid pCGN8520 was cut with *Xho*I and *Bgl*II and ligated to pCGN7770 after digestion with *Sal*I and *Bgl*II. The resultant napin/ORF 3 gene fusion plasmid was designated pCGN8528. Plasmid pCGN7773 was cut with *Sal*I and *Bam*HI and ligated to pCGN7770 after digestion with *Sal*I and *Bgl*II. The resultant napin/ORF 9 gene fusion plasmid was designated pCGN7785. Plasmid pCGN7775A was cut with *Sal*I and ligated to pCGN7770 after digestion with *Sal*I. The resultant napin/ORF 8 gene fusion plasmid was designated pCGN7782. Plasmid pCGN7776B4 was cut with *Xho*I and ligated to pCGN7770 after digestion with *Sal*I. The resultant napin/ORF 6 gene fusion plasmid was designated pCGN7786B4.

A binary vector for plant transformation, pCGN5139, was constructed from pCGN1558 (McBride and Summerfelt (1990) *Plant Molecular Biology*, 14:269-276). The polylinker of pCGN1558 was replaced as a *Hin*dIII/*Asp*718 fragment with a polylinker containing unique restriction endonuclease sites, *Asc*I, *Pac*I, *Xba*I, *Swa*I, *Bam*HI, and*Not*I. The *Asp*718 and *Hin*dIII restriction endonuclease sites are retained in pCGN5139. PCGN5139 was digested with *Not*I and ligated with *Not*I digested pCGN7786B4. The resultant binary vector containing the napin/ORF 6 gene fusion was designated pCGN8533. Plasmid pCGN8533 was digested with *Sse*8387I and ligated with *Sse*8387I digested pCGN7782. The resultant binary vector containing the napin/ORF 6 gene fusion and the napin/ORF 8 gene fusion was designated pCGN8535 (Figure 18).

The plant binary transformation vector, pCGN5139, was digested with *Asp*718 and ligated with *Asp*718 digested pCGN8528. The resultant binary vector containing the napin/ORF 3 gene fusion was designated pCGN8532. Plasmid pCGN8532 was digested with *Not*I and ligated with *Not*I digested pCGN7783. The resultant binary vector containing the napin/ORF 3 gene fusion and the napin/ORF 7 gene fusion was designated pCGN8534. Plasmid pCGN8534 was digested with *Sse*8387I and ligated with *Sse*8387I digested pCGN7785. The resultant binary vector containing the napin/ORF 3 gene fusion, the napin/ORF 7 gene fusion and the napin/ORF 9 gene fusion was designated pCGN8537 (Figure 19).

Vibrio constructs

The *Vibrio* ORFs for plant expression were all obtained using *Vibrio* cosmid #9 as a starting molecule. *Vibrio* cosmid #9 was one of the cosmids isolated from the *Vibrio* cosmid library using the *Vibrio* ORF 6 PCR product described in Example 1.

A gene encoding *Vibrio* ORF 7 (Figure 6) was mutagenized to introduce a *Sal*I site upstream of the open reading frame and *Bam*HI site downstream of the open reading frame using the PCR primers: TCTAGAGTCGACACAATGGCGGAATTAGCTG TTATTGGT and GTCGACGGATCCCTATTTGTTCGTGTTTGCTATATG. A gene encoding *Vibrio* ORF 9 (Figure 6) was mutagenized to introduce a *Bam*HI site upstream of the open reading frame and an *Xho*HI site downstream of the open reading frame using the PCR primers: GTCGACGGATCCACAATGAATATAGTAAGTAATCATTCGGCA and GTCGACCTCGAGTTAATCACTCGTACGATAACTTGCC. The restriction sites were introduced using PCR, and the integrity of the mutagenized plasmids was verified by DNA sequence. The *Vibrio* ORF 7 gene was cloned as a *Sal*I-*Bam*HI fragment into the napin cassette of *Sal-Bgl*I digested pCGN7770 (Figure 17) to yield pCGN8539. The *Vibrio* ORF 9 gene was cloned as a *Sal*I-*Bam*HI fragment into the napin cassette of *Sal-Bal*I digested pCGN7770 (Figure 17) to yield pCGN8543.

Genes encoding the *Vibrio* ORF 6 and ORF 8 were mutagenized to introduce *Sal*I sites flanking the open reading frames. The *Sal*I sites flanking ORF 6 were introduced using PCR. The primers used were: CCCGGGTCGACACAATGGCTAAAAAGAACA CCACATCGA and CCCGGGTCGACTCATGACATATCGTTCAAAATGTCACTGA. The central 7.3 kb *Bam*HI-*Xho*I fragment of the PCR product was replaced with the corresponding fragment from *Vibrio* cosmid #9. The mutagenized ORF 6 were cloned into the *Sal*I site of the napin cassette of pCGN7770 to yield plasmid pCGN8554.

The mutagenesis of ORF 8 used a different strategy. A *Bam*HI fragment containing ORF 8 was subcloned into plasmid pHC79 to yield cosmid #9". A *Sal*I site upstream of the coding region was introduced on and adapter comprised of the oligonucleotides TCGACATGGAAAATATTGCAGTAGTAGGTATTGCTAATTT GTTC and CCGGGAACAAATTAGCAATACCTACTACTGCAATATTTTCCATG. The adapter was ligated to cosmid #9" after digestion with *Sal*I and *Xma*I. A *Sal*I site was introduced downstream of the stop codon by using PCR for mutagenesis. A DNA fragment containing the stop codon was generated using cosmid #9" as a template with the primers TCAGATGAACTTTATCGATAC and TCATGAGACGTCGTCGACTTA

CGCTTCAACAATACT. The PCR product was digested with the restriction endonucleases *Cla*I and *Aat*II and was cloned into the cosmid 9" derivative digested with the same enzymes to yield plasmid 8P3. The *Sal*I fragment from 8P3 was cloned into *Sal*I digested pCGN7770 to yield pCGN8515.

PCGN8532, a binary plant transformation vector that contains a *Shewannella* ORF 3 under control of the napin promoter was digested with *Not*I, and a *Not*I fragment of pCGN8539 containing a napin *Vibrio* ORF 7 gene fusion was inserted to yield pCGN8552. Plasmid pCGN8556 (Figure 23), which contains *Shewannella* ORF 3, and *Vibrio* ORFs 7 and 9 under control of the napin promoter was constructed by cloning the *Sse*8357 fragment from pCGN8543 into *Sse*8387 digested pCGN8552.

The *Not*I digested napin/ORF 8 gene from plasmid pCGN8515 was cloned into a *Not*I digested plant binary transformation vector pCGN5139 to yield pCGN8548. The *Sse*8387 digested napin/ORF 6 gene from pCGN8554 was subsequently cloned into the *Sse*8387 site of pCGN8566. The resultant binary vector containing the napin/ORF 6 gene fusion and napin/ORF 8 gene fusion was designated pCGN8560 (Figure 22).

Example 5

Plant Transformation and PUFA Production

EPA production

The *Shewanella* constructs pCGN8535 and pCGN8537 can be transformed into the same or separate plants. If separate plants are used, the transgenic plants can be crossed resulting in heterozygous seed which contains both constructs.

pCGN8535 and pCGN8537 are separately transformed into *Brassica napus*. Plants are selected on media containing kanamycin and transformation by full length inserts of the constructs is verified by Southern analysis. Immature seeds also can be tested for protein expression of the enzyme encoded by ORFs 3, 6, 7, 8, or 9 using western analysis, in which case, the best expressing pCGNE8535 and pCGN8537 T_1 transformed plants are chosen and are grown out for further experimentation and crossing. Alternatively, the T_1 transformed plants showing insertion by Southern are crossed to one another producing T_2 seed which has both insertions. In this seed, half seeds may be analyzed directly from expression of EPA in the fatty acid fraction. Remaining half-seed

of events with the best EPA production are grown out and developed through conventional breeding techniques to provide *Brassica* lines for production of EPA.

Plasmids pCGN7792 and pCGN7795 also are simultaneously introduced into *Brassica napus* host cells. A standard transformation protocol is used (*see* for example USPN 5,463,174 and USPN 5,750,871, however *Agrobacteria* containing both plasmids are mixed together and incubated with *Brassica* cotyledons during the cocultivation step. Many of the resultant plants are transformed with both plasmids.

DHA production

A plant is transformed for production of DHA by introducing pCGN8556 and pCGN8560, either into separate plants or simultaneously into the same plants as described for EPA production.

Alternatively, the *Shewanella* ORFs can be used in a concerted fashion with ORFs 6 and 8 of *Vibrio*; such as by transforming with a plant the constructs pCGN8560 and pCGN7795, allowing expression of the corresponding ORFs in a plant cell. This combination provides a PKS-like gene arrangement comprising ORFs 3, 7 and 9 of *Shewanella*, with an ORF 6 derived from *Vibrio* and also an OFR 8 derived from *Vibrio*. As described above, ORF 8 is the PKS-like gene which controls the identity of the final PUFA product. Thus, the resulting transformed plants produce DHA in plant oil.

Example 6

Transgenic plants containing the *Shewanella* PUFA genes

Brassica plants

Fifty-two plants cotransformed with plasmids pCGN8535 andpCGN8537 were analyzed using PCR to determine if the *Shewanella* ORFs were present in the transgenic plants. Forty-one plants contained plasmid pCGN8537, and thirty-five plants contained pCGN8535. 11 of the plants contained all five ORFs required for the synthesis of EPA. Several plants contained genes from both of the binary plasmids but appeared to be missing at least one of the ORFs. Analysis is currently being performed on approximately twenty additional plants.

Twenty-three plants transformed with pCGN8535 alone were analyzed using PCR to determine if the *Shewanella* ORFs were present in the transgenic plants. Thirteen of

these plants contained both *Shewanella* ORF 6 and *Shewanella* ORF 8. Six of the plants contained only one ORF.

Nineteen plants transformed with pCGN8537 were alone analyzed using PCR to determine if the *Shewanella* ORFs were present in the transgenic plants. Eighteen of the plants contained *Shewanella* ORF 3, *Shewanella* ORF 7, and *Shewanella* ORF 9. One plant contained *Shewanella* ORFs 3 and 7.

Arabidopsis

More than 40 transgenic Arabidopsis plants cotransformed with plasmids pCGN8535 and pCGN8537 are growing in our growth chambers. PCR analysis to determine which of the ORFs are present in the plants is currently underway.

By the present invention PKS-like genes from various organisms can now be used to transform plant cells and modify the fatty acid compositions of plant cell membranes or plant seed oils through the biosynthesis of PUFAs in the transformed plant cells. Due to the nature of the PKS-like systems, fatty acid end-products produced in the plant cells can be selected or designed to contain a number of specific chemical structures. For example, the fatty acids can comprise the following variants: Variations in the numbers of keto or hydroxyl groups at various positions along the carbon chain; variations in the numbers and types (*cis* or *trans*) of double bonds; variations in the numbers and types of branches off of the linear carbon chain (methyl, ethyl, or longer branched moieties); and variations in saturated carbons. In addition, the particular length of the end-product fatty acid can be controlled by the particular PKS-like genes utilized.

All publications and patent applications mentioned in this specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the appended claims.

What is claimed is:

1. An isolated nucleic acid comprising:

a *Vibrio marinus* nucleotide sequence selected from the group consisting of the ORF 6, ORF 7, ORF 8 and ORF 9 as shown in Figure 6.

2. An isolated nucleic acid comprising:

a nucleotide sequence which encodes a polypeptide of a polyketide-like synthesis system, wherein said system produces a docosahexenoic acid when expressed in a host cell.

3. The isolated nucleic acid according to Claim 2, wherein said nucleotide sequence is derived from a marine bacterium.

4. The isolated nucleic acid according to Claim 2, wherein said nucleotide sequence is a *Vibrio marinus* ORF 8 as shown in Figure 6.

5. An isolated nucleic acid comprising:

a nucleotide sequence which is substantially identical to a sequence of at least 50 nucleotides of a *Vibrio marinus* nucleotide sequence selected from the group consisting of ORF 6, ORF 7, ORF 8 and ORF 9 as shown in Figure 6.

6. A recombinant microbial cell comprising at least one copy of an isolated nucleic acid according to Claim 1 or Claim 2.

7. The recombinant microbial cell according to Claim 6, wherein said cell comprises each element of a polyketide-like synthesis system required to produce a long chain polyunsaturated fatty acid.

8. The recombinant microbial cell according to Claim 7, wherein said cell is a eukaryotic cell.

9. The recombinant microbial cell according to Claim 8, wherein said eukaryotic cell is a fungal cell, an algae cell or an animal cell.

10. The recombinant microbial cell according to Claim 9, wherein said fungal cell is a yeast cell and said algae cell is a marine algae cell.

11. The recombinant microbial cell according to Claim 6, wherein said cell is a prokaryotic cell.

12. The recombinant microbial cell according to Claim 11, wherein said cell is a bacterial cell or a cyanobacterial cell.

13. The microbial cell according to Claim 6, wherein said recombinant microbial cell is enriched for 22:6 fatty acids as compared to a non-recombinant microbial cell which is devoid of said isolated nucleic acid.

14. A method for production of docosahexenoic acid in a microbial cell culture, said method comprising:

growing a microbial cell culture having a plurality of microbial cells, wherein said microbial cells or ancestors of said microbial cells were transformed with a vector comprising one or more nucleic acids having a nucleotide sequence which encodes a polypeptide of a polyketide synthesizing system, wherein said one or more nucleic acids are operably linked to a promoter, under conditions whereby said one or more nucleic acids are expressed and docosahexenoic acid is produced in said microbial cell culture.

15. A method for production of a long chain polyunsaturated fatty acid in a plant cell, said method comprising:

growing a plant having a plurality of plant cells, wherein said plant cells or ancestors of said plant cells were transformed with a vector comprising one or more nucleic acids having a nucleotide sequence which encodes one or more polypeptides of a polyketide synthesizing system which produces a long chain polyunsaturated fatty acid, wherein each of said nucleic acids are operably linked to a promoter functional in a plant cell, under conditions whereby said polypeptides are expressed and a long chain polyunsaturated fatty acid is produced in said plant cells.

16. The method according to Claim 15, wherein said long chain polyunsaturated fatty acid produced in said plant cells is a 20:5 and 22:6 fatty acid.

17. The method according to Claim 15, wherein said nucleic acids comprise nucleotide sequences encoding any one of the polypeptides selected from the group consisting of *Vibrio marinus* ORF 6, ORF 7, ORF 8 and ORF 9 as shown in Figure 6 and *Shewanella putrefaciens* ORF 3, ORF 6, ORF 7, ORF 8 and ORF 9 as shown in Figure 4.

18. The method according to Claim 15, wherein said nucleic acid constructs are derived from two or more polyketide synthesizing systems.

19. A recombinant plant cell which produces an long chain polyunsaturated fatty acid exogenous to said plant cell, wherein said recombinant plant cell is produced according to a method comprising:

transforming a plant cell or an ancestor or said plant cell with a vector comprising one or more nucleic acids having a nucleotide sequence which encodes one or more polypeptides of a polyketide synthesizing system which produces a long chain polyunsaturated fatty acid, wherein each of said nucleic acids are operably linked to a promoter functional in said plant cell whereby a recombinant plant cell is obtained; and

growing said recombinant plant cell under conditions whereby said polypeptides are expressed and a long chain polyunsaturated fatty acid is produced in said plant cell.

20. The recombinant plant cell according to Claim 19, wherein said recombinant plant cell is a recombinant seed cell.

21. The recombinant plant cell according to Claim 20, wherein said recombinant seed cell is a recombinant embryo cell.

22. The method according to Claim 15, wherein said long chain polyunsaturated fatty acid produced in said plant cells is eicosapentenoic acid.

23. The method according to Claim 15, wherein said long chain polyunsaturated fatty acid produced in said plant cells is docosahexenoic acid.

24. The recombinant plant cell according to Claim 19, wherein said recombinant plant cell is from a plant selected from the group consisting of *Brassica*, soybean, safflower, and sunflower.

25. A plant oil produced by a recombinant plant cell according to Claim 19, wherein said plant oil comprises eicosapentenoic acid.

26. A plant oil produced by a recombinant plant cell according to Claim 19, wherein said plant oil comprises docosahexenoic acid.

27. The plant oil according to Claim 25 or Claim 26, wherein said plant oil is encapsulated.

28. A dietary supplement comprising a plant oil according to Claim 27.

29. A recombinant *E. coli* cell which produces docosahexenoic acid.

30. A plant oil comprising eicosapentenoic acid.

31. A plant oil comprising docosahexenoic acid.

32. The recombinant microbial cell according to Claim 12, wherein said bacterial cell is a lactobacillus cell.

Fig. 1 Organization of Shewanella EPA Genes and Clones Obtained from the Sagami Chemical Institute.

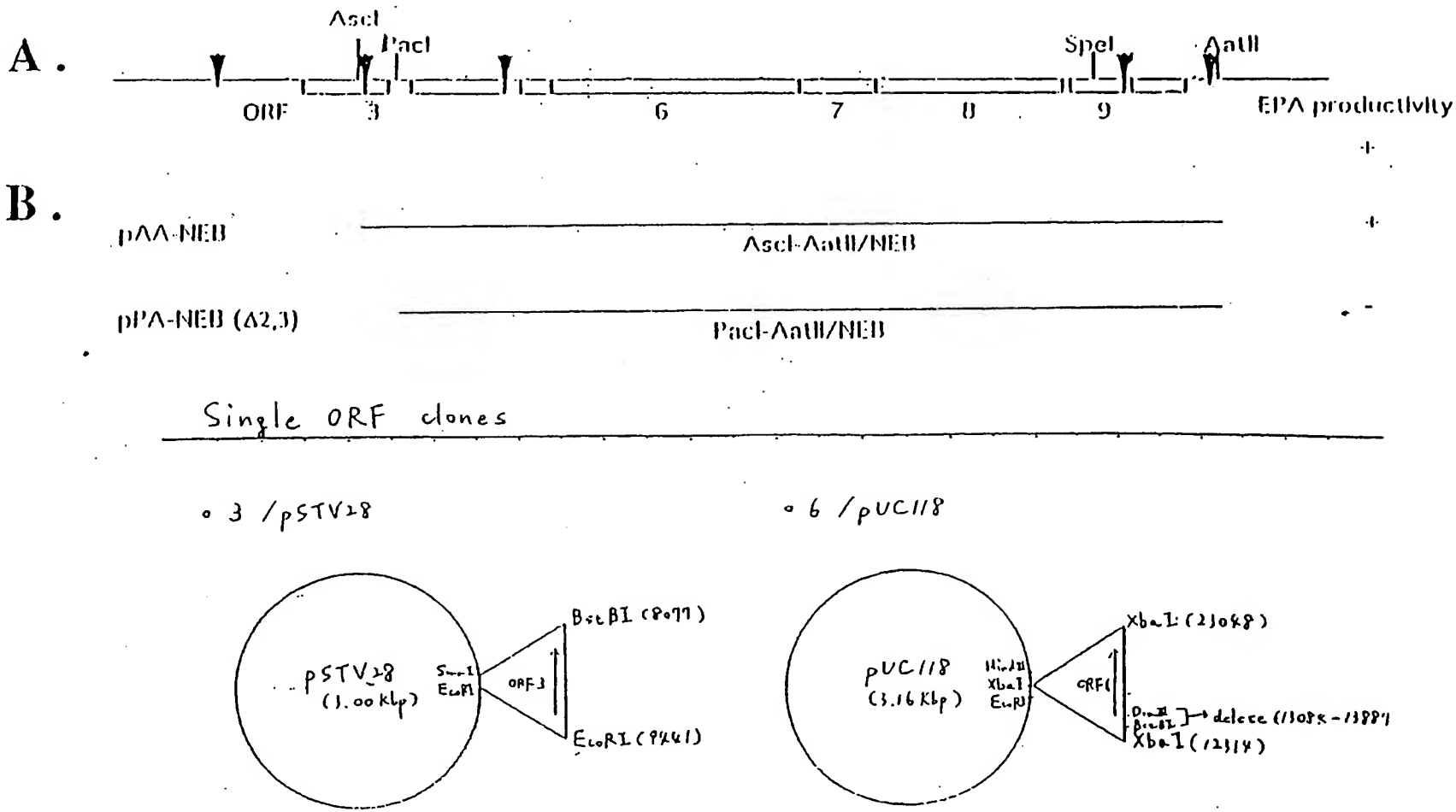


Fig. 2 SHEWANELLA EPA ORFs

Motifs - Domains - Homologies

Orf6 8.3 KB - 293 kD

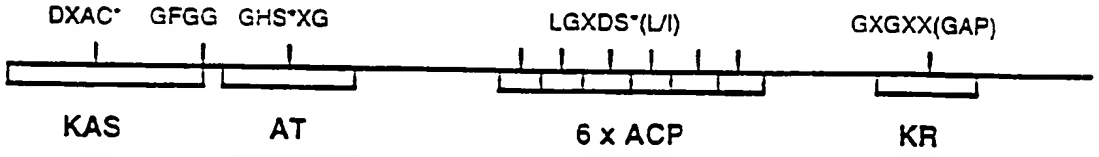


FIG 2A

Orf7 2.3 KB - 84 kD

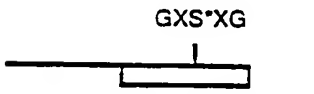


FIG 2B

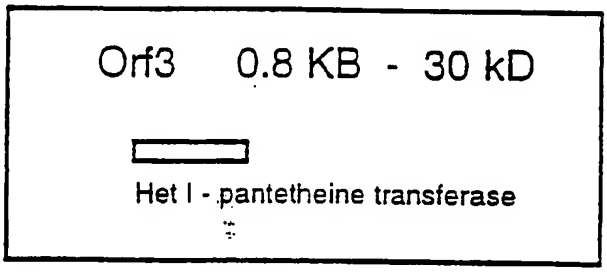


FIG 2E

Orf8 6.0 KB - 217 kD

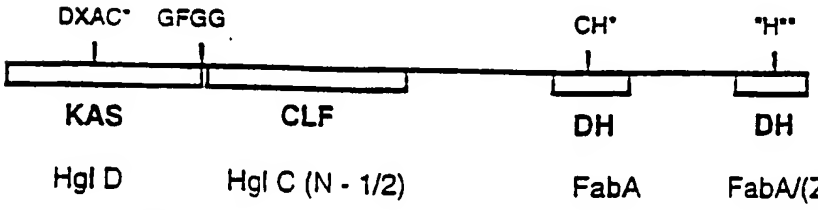
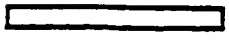


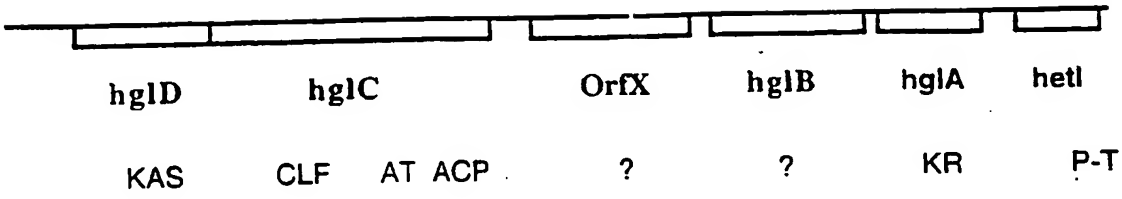
FIG 2C

Orf9 1.6 KB - 59 kD



Anabeana - OrfX homolog

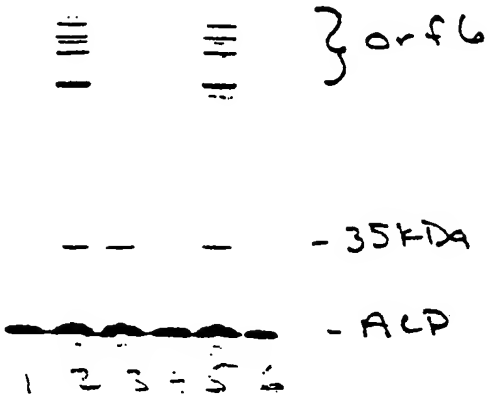
FIG 2D



Anabeana "PKS" Genes Involved in Heterocyst Glycolipid Synthesis**

Fig 3. Orf3 Encodes a Phosphopantetheine Transferase

1. pUC19
3. pAA-Neb (EPA +)
2. pPA-NEB (Δ Orf3)
4. Orf6 subclone
5. Orf6 + Orf3 subclones
6. Orf3 subclone



Autoradiograph of [C14] ß-Alanine labelled proteins from *E. coli* (strain SJ16) cells transformed with the above listed plasmids. Cells were grown in the presence of [C14] ß-alanine and the appropriate antibiotics. Proteins were extracted, separated by SDS-PAGE and transferred to a PVDF membrane prior to autoradiography. ACP and an unknown (but previously observed) 35 kD protein were labelled in all of the samples. The high molecular mass proteins detected in lanes 2 and 5 are full-length (largest band) and truncated products of the Shewanella Orf6 gene (confirmed by Western analysis - data not shown). *E. coli* strain SJ16 is conditionally blocked in ß-alanine synthesis.

Sequence Range: 1 to 37895

```
                   20                  40                  60                  80
GATCTCTTAC AAAGAAACTA TCTCAATGTG AATTTAACCT TAATTCCGTT TAATTACGGC CTGATAGAGC ATCACCCAAT
                  100                 120                 140                 160
CAGCCATAAA ACTGTAAAGT GGGTACTCAA AGGTGGCTGG GCGATTCTTC TCAAATACAA AGTGCCCAAC CCAAGCAAAT
                  180                 200                 220                 240
CCATATCCGA TAACAGGTAA AAGTAGCAAT AAACCCCAGC GCTGAGTTAG TAATACATAA GCGAATAATA GGATCACTAA
                  260                 280                 300                 320
ACTACTGCCG AAATAGTGTA ATATTCGACA GTTTCTATGC TGATGTTGAG ATAAATAAAA AGGGTAAAAT TCAGCAAAAG
                  340                 360                 380                 400
AACGATAGCG CTTACTCATT ACTCACACCT CGGTAAAAAA GCAACTCGCC ATTAACTTGG CCAATCGTCA GTTGTTCTAT
                  420                 440                 460                 480
CGTCTCAAAG TTATGCCGAC TAAATAACTC TATATGTGCA TTATGATTAG CAAAAACTCC GATACCATCA AGATGAAGTT
                  500                 520                 540                 560
GTTCATCACA CCAACTCAAA ACTGCGTCGA TAAGCTTACT GCCATAGCCC TTGCCTTGCT CCACATTTGC GATAGCAATA
                  580                 600                 620                 640
AACTGTAAAA TGCCACATTG GCCACTTGGT AAGCTCTCTA TAATCTGATT TTCTTTGTTA ATAAGTGCCT GAGTTGAATA
                  660                 680                 700                 720
CCAACCAGTA CTTAACAACA TCTTTAAACG CCAATGCCAA AAACCCGCTT CACCTAAGGG AACCTGCTGA GTCACTATGC
                  740                 760                 780                 800
AGGCTACGCC TATCAATCTA TCCCCAACGA ACATACCAAT AAGTGCTTGC TCCTGTTGCC AGAGCTCATT GAGTTCTTCT
                  820                 840                 860                 880
CGAATAGCCC CGCGAAGCTT TTGCTCATAC TGCGCTTGAT CACCACTAAA AAGTGTTTCG ATAAAAAAGG GATCATCATG
                  900                 920                 940                 960
ATAGGCGTTA TAGAGAATAG AGGCTGCTAT GCGTAAATCT TCTGCCGTGA GATAAACTGC ACGACACTCT TCCATGGCTT
                  980                1000                1020                1040
GATCTTCCAT TGTTATTGTC CTTGACCTTG ATCACACAAC ACCAATGTAA CAAGACTGTA TAGAAGTGCA ATTAATAATC
                 1060                1080                1100                1120
AATTCGTGCA TTAAGCAGGT CAGCATTTCT TTGCTAAACA AGCTTTATTG GCTTTGACAA AACTTTGCCT AGACTTTAAC
                 1140                1160                1180                1200
GATAGAAATC ATAATGAAAG AGAAAAGCTA CAACCTAGAG GGGAATAATC AAACAACTGC TAAGATCTAG ATAATGTAAT
                 1220                1240                1260                1280
AAACACCGAG TTTATCGACC ATACTTAGAT AGAGTCATAG CAACGAGAAT AGTTATGGAT ACAACGCCGC AAGATCTATC
                 1300                1320                1340                1360
ACACCTGTTT TTACAGCTAG GATTAGCAAA TGATCAACCC GCAATTGAAC AGTTTATCAA TGACCATCAA TTAGCGGACA
                 1380                1400                1420                1440
ATATATTGCT ACATCAAGCA AGCTTTTGGA GCCCATCGCA AAAGCACTTC TTAATTGAGT CATTTAATGA AGATGCCCAG
                 1460                1480                1500                1520
TGGACCGAAG TCATCGACCA CTTAGACACC TTATTAAGAA AAAACTAACC ATTACAACAG CAACTTTAAA TTTTGCCGTA
                 1540                1560                1580                1600
AGCCATCTCC CCCCACCCCA CAACAGCGTT GTTGCTTATG ACCACTGGAG TACATTCGTC TTTAGTCGTT TTACCATCAC
                 1620                1640                1660                1680
CATGGGTACG TTGAGTGCGA TAAAAAAGCA CATAAACTTC TTTATCGGCC TGAATATAGG CTTCGTTAAA ATCAGCTGTT
                 1700                1720                1740                1760
CCCATTAAAG TAACCACTTG CTCTTTACTC ATGCCTAGAG ATATCTTTGT CAAATTGTCA CGGTTTTTAT CTTGAGTTTT
```

Fig. 4
1/30

```
                1780                1800                1820                1840
CTCCCAAGCA CCGTGATTAT CCCAGTCAGA TTCCCCATCA CCAACATTGA CCACACAGCC CGTTAGCCCT AAGCTTGCAA

                1860                1880                1900                1920
TCCCAAAACA TGCTAAACCT AATAATTTAT TTTTCATTTT AACTTCCTGT TATGACATTA TTTTTGCTTA GAAGAAAAGC

                1940                1960                1980                2000
AACTTACATG CCAAAACACA AGCTGTTGTT TTAAATGACT TTATTTATTA TTAGCCTTTT AGGATATGCC TAGAGCAATA

                2020                2040                2060                2080
ATAATTACCA ATGTTTAAGG AATTTGACTA ACTATGAGTC CGATTGAGCA AGTGCTAACA GCTGCTAAAA AAATCAATGA

                2100                2120                2140                2160
ACAAGGTAGA GAACCAACAT TAGCATTGAT TAAAACCAAA CTTGGTAATA GCATCCCAAT GCGCGAGTTA ATCCAAGGTT

                2180                2200                2220                2240
TGCAACAGTT TAAGTCTATG AGTGCAGAAG AAAGACAAGC AATACCTAGC AGCTTAGCAA CAGCAAAAGA AACTCAATAT

                2260                2280                2300                2320
GGTCAATCAA GCTTATCTCA ATCTGAACAA GCTGATAGGA TCCTCCAGCT AGAAAACGCC CTCAATGAAT TAAGAAACGA

                2340                2360                2380                2400
ATTTAATGGG CTAAAAAGTC AATTTGATAA CTTACAACAA AACCTGATGA ATAAAGAGCC TGACACCAAA TGCATGTAAT

                2420                2440                2460                2480
TGAACTACGA TTTGAATGTT TTGATAACAC CACGATTACT GCAGCAGAAA AAGCCATTAA TGGTTTGCTT GAAGCTTATC

                2500                2520                2540                2560
GAGCCAATGG CCAGGTTCTA GGTCGTGAAT TTGCCGTTGC ATTTAACGAT GGTGAGTTTA AAGCACGCAT GTTAACCCCA

                2580                2600                2620                2640
GAAAAAAGCA GCTTATCTAA ACGCTTTAAT AGTCCTTGGG TAAATAGTGC ACTCGAAGAG CTAACCGAAG CCAAATTGCT

                2660                2680                2700                2720
TGCGCCACGT GAAAAGTATA TTGGCCAAGA TATTAATTCT GAAGCATCTA GCCAAGACAC ACCAAGTTGG CAGCTACTTT

                2740                2760                2780                2800
ACACAAGTTA TGTGCACATG TGCTCACCAC TAAGAAATGG CGACACCTTG CAGCCTATTC CACTGTATCA AATTCCAGCA

                2820                2840                2860                2880
ACTGCCAACG GCGATCATAA ACGAATGATC CGTTGGCAAA CAGAATGGCA AGCTTGTGAT GAATTGCAAA TGGCCGCAGC

                2900                2920                2940                2960
TACTAAAGCT GAATTTGCCG CACTTGAAGA GCTAACCAGT CATCAGAGTG ATCTATTTAG GCGTGGTTGG GACTTACGTG

                2980                3000                3020                3040
GCAGAGTCGA ATACTTGACG AAAATTCCGA CCTATTACTA TTTATACCGT GTTGGCGGTG AAAGCTTAGC AGTAGAAAAG

                3060                3080                3100                3120
CAGCGCTCTT GTCCTAAGTG TGGCAGTCAA GAATGGCTGC TCGATAAACC ATTATTGGAT ATGTTCCATT TTCGCTGTGA

                3140                3160                3180                3200
CACCTGCCGC ATCGTATCTA ATATCTCTTG GGACCATTTA TAACTCTTCC GAGTCTTATC ACACTAGAGT TTAGTCAGCA

                3220                3240                3260                3280
TAAAAATGGC GCTTATATTT CAATTAAAAG AAATATAAGC GCCATTTTCA TCGATACTAT ATATCAGCAG ACTATTTTCC

                3300                3320                3340                3360
GCGTAAATTA GCCCACATTA ATTTCATTCT TTGCCAGATC CCTGGATGAT CTAGTTGTGG CATCGACTCT TCAATAGGTT

                3380                3400                3420                3440
TAACCGCAGG TGTAACCCTT GGAGTCAATT CGTTTATAAA CTCGTTTAAA CTGTCACTTA ATTTAACGCT TTGTACTTCA

                3460                3480                3500                3520
CCTGGAATTT CAATCCATAC GCTGCCATCA CTATTATTAA CCGTCAACAT TTTATCTTCA TCATCAAGAA TACCAATAAA
```

Fig. 4
2/30

```
                3540                3560                3580                3600
CCAAGTCGGC TCTTGCTTAA GCTTTCTCTT CATCATTAAA TGACCAATGA TGTTTTGTTG TAAGTATTCA AAATCAGTTT
                3620                3640                3660                3680
GATCCCACAC TTGGATTAGC TCACCTTGGC CCCATTGTGA GTCAAAAAAT AGCGGTGCAG AAAAATGACT GCCAAAAAAT
                3700                3720                3740                3760
GGATTAATTT CTGCAGATAA TGTCATTTCA AGTGCTGTTT CAACATTAGC AAATTCACCA GGTTGTTGAC GTACAACCGA
                3780                3800                3820                3840
TTGCCAAAAC ACTGCGCCAT CGGAGCCCGC TTCGGCGACA ACACACTCAG ACTTTTGTCC TTGCGCATAA TATCTTGGCT
                3860                3880                3900                3920
GTTCACCAAG CTTATCCATG TAGGCTTGTT GATATTTAGA TAAAAAAAGA TCTAAAGCAG GTAAAGAAGA CACTTAAGCC
                3940                3960                3980                4000
AGTTCCAAAA TCAGTTATAA TAGGGGTCTA TTTTGACATG GAAACCGTAT TGATGACACA ACATCATGAT CCCTACAGTA
                4020                4040                4060                4080
ACGCCCCCGA ACTTTCTGAA TTAACTTTAG GAAAGTCGAC CGGTTATCAA GAGCAGTATG ATGCATCTTT ACTACAAGCG
                4100                4120                4140                4160
TGCCGCGTAA ATTAAACCGT GATGCTATCG GTCTAACCAA TGAGCTACCT TTTCATGGCT GTGATATTTG GACTGGCTAC
                4180                4200                4220                4240
GAACTGTCTT GGCTAAATGC TAAAGGCAAG CCAATGATTG CTATTGCAGA CTTTAACCTA AGTTTTGATA GTAAAAATCT
                4260                4280                4300                4320
GATCGAGTCT AAGTCGTTTA AGCTGTATTT AAACAGCTAT AACCAAACAC GATTTGATAG CGTTCAAGCG GTTCAAGAAC
                4340                4360                4380                4400
GTTTAACTGA AGACTTAAGC GCCTGTGCCC AAGGCACAGT TACGGTAAAA GTGATTGAAC CTAAGCAATT TAACCACCTG
                4420                4440                4460                4480
AGAGTGGTTG ATATGCCAGG TACCTGCATT GACGATTTAG ATATTGAAGT TGATGACTAT AGCTTTAACT CTGACTATCT
                4500                4520                4540                4560
CACCGACAGT GTTGATGACA AAGTCATGGT TGCTGAAACG CTAACGTCAA ACTTATTGAA ATCAAACTGC CTAATCACTT
                4580                4600                4620                4640
CTCAGCCTGA CTGGGGTACA GTGATGATCC GTTATCAAGG GCCTAAGATA GACCGTGAAA AGCTACTTAG ATATCTGATT
                4660                4680                4700                4720
TCATTTAGAC AGCACAATGA ATTTCATGAG CAGTGTGTTG AGCGTATATT TGTTGATTTA AAGCACTATT GCCAATGTGC
                4740                4760                4780                4800
CAAACTTACT GTCTATGCAC GTTATACCCG CCGTGGTGGT TTAGATATCA ACCCATATCG TAGCGACTTT GAAAACCCTG
                4820                4840                4860                4880
CAGAAAATCA GCGCCTAGCG AGACAGTAAT TGATTGCAGT ACCTACAAAA AACAATGCCT ATAAGCCAAG CTTATGGGCA
                4900                4920                4940                4960
TTTTTATATT ATCAACTTGT CATCAAACCT CAGCCGCCAA GCCTTTTAGT TTTATCGCTA AATTAAGCCG CTCTCTCAGC
                4980                5000                5020                5040
CAAATATTTG CAGGATTTTG CTGTAATTTA TGGCTCCACA CCATGAAATA CTCTATCGGC TCTACCGCAA AAGGTAAGTC
                5060                5080                5100                5120
AAATACCTGT AAGCCAAACA GCTTGGCATA TTCGTCAGTG TGGGCTTTTG ACGCGATAGC TAACGCATCA CTTTTTGAGG
                5140                5160                5180                5200
CAACCGACAT CATACTTAAT ATTGATGATT GCTCGCTGTG CATTTGCCTT GCCGGTAACA CCTGTTTAGT CAGCAAGTCG
                5220                5240                5260                5280
GCAACACTTA AATTGTAGCG GCGCATCTTA AAAATAATAT GCTTTTCATT AAAGTATTGC TCTTGCGTCA ACCCACCTTG
                5300                5320                5340                5360
```

Fig 4
3/30

```
GATCCTTGGG TGAGCATTTC GTGCCACACA AACTAATTTA TCCTGCATTA CTTTTTGACT CTTAAATGCC GCAGATTCTG

                5380                5400                5420                5440
GCAGCCAAAT ATCTAAGGCT AAATCCACCT TTTCTAGTTG TAGGTCCATC TGCAACTCTT CTTCAATGAG CGGCGGCTCA

                5460                5480                5500                5520
CGAAATACAA TATTAATTGC AGTGCCCTGT AACACTTGCT CAATTTGATC TTGCAAGAGT TGTATTGCCG ACTCGCTGGC

                5540                5560                5580                5600
ATACACATAA AAAGTTCGCT CACTTGAAGT GGGGTCAAAT GCTTCAAAGC TAGTCGCAAC TTGCTCAATT GTTGACATAG

                5620                5640                5660                5680
CGCCCGCGAG CTGTTGATAA AGCGTCATCG CACTTGCGGT AGGTTTAACT CCCCTACCCA CTCGAGTAAA CAACTCTTCT

                5700                5720                5740                5760
CCAACAATAC TTTTTAGCCT CGAAATCGCA TTACTAACCG ACGACTGAGT CAAATCCAGC TCTTCTGCCG CCCGGCTAAA

                5780                5800                5820                5840
AGATGAGGTG CGATACACCG CAGTAAAAAC GCGAAATAAA TTAAGATCAA AAGCTTTTTG CTGCGACATA AATCAGCTAT

                5860                5880                5900                5920
CTCCTTATCC TTATCCTTAT CCTTATAAAA AGTTAGCTCC AGAGCACTCT AGCTCAAAAA CAACTCAGCG TATTAAGCCA

                5940                5960                5980                6000
ATATTTTGGG AACTCAATTA ATATTCATAA TAAAAGTATT CATAATATAA ATACCAAGTC ATAATTTAGC CCTAATTATT

                6020                6040                6060                6080
AATCAATTCA AGTTACCTAT ACTGGCCTCA ATTAAGCAAA TGTCTCATCA GTCTCCCTGC AACTAAATGC AATATTGAGA

                6100                6120                6140
CATAAAGCTT TGAACTGATT CAATCTTACG ACGGTAACTT ATG AAA CAG ACT CTA ATG GCT ATC TCA ATC ATG
                                          M   K   Q   T   L   M   A   I   S   I   M>

      6160                6180                6200
TCG CTT TTT TCA TTC AAT GCG CTA GCA GCG CAA CAT GAA CAT GAC CAC ATC ACT GTT GAT TAC GAA
 S   L   F   S   F   N   A   L   A   A   Q   H   E   H   D   H   I   T   V   D   Y   E>

6220                6240                6260                6280
GGG AAA GCC GCA ACA GAA CAC ACC ATA GCT CAC AAC CAA GCT GTA GCT AAA ACA CTT AAC TTT GCC
 G   K   A   A   T   E   H   T   I   A   H   N   Q   A   V   A   K   T   L   N   F   A>

            6300                6320                6340
GAC ACG CGT GCA TTT GAG CAA TCG TCT AAA AAT CTA GTC GCC AAG TTT GAT AAA GCA ACT GCC GAT
 D   T   R   A   F   E   Q   S   S   K   N   L   V   A   K   F   D   K   A   T   A   D>

      6360                6380                6400
ATA TTA CGT GCC GAA TTT GCT TTT ATT AGC GAT GAA ATC CCT GAC TCG GTT AAC CCG TCT CTC TAC
 I   L   R   A   E   F   A   F   I   S   D   E   I   P   D   S   V   N   P   S   L   Y>

6420                6440                6460                6480
CGT CAG GCT CAG CTT AAT ATG GTG CCT AAT GGT CTG TAT AAA GTG AGC GAT GGC ATT TAC CAG GTC
 R   Q   A   Q   L   N   M   V   P   N   G   L   Y   K   V   S   D   G   I   Y   Q   V>

                6500                6520                6540
CGC GGT ACC GAC TTA TCT AAC CTT ACA CTT ATC CGC AGT GAT AAC GGT TGG ATA GCA TAC GAT GTT
 R   G   T   D   L   S   N   L   T   L   I   R   S   D   N   G   W   I   A   Y   D   V>

          6560                6580                6600
TTG TTA ACC AAA GAA GCA GCA AAA GCC TCA CTA CAA TTT GCG TTA AAG AAT CTA CCT AAA GAT GGC
 L   L   T   K   E   A   A   K   A   S   L   Q   F   A   L   K   N   L   P   K   D   G>

  6620                6640                6660                6680
GAT TTA CCC GTT GTT GCG ATG ATT TAC TCC CAT AGC CAT GCG GAC CAC TTT GGC GGA GCT CGC GGT
 D   L   P   V   V   A   M   I   Y   S   H   S   H   A   D   H   F   G   G   A   R   G>

                6700                6720                6740
GTT CAA GAG ATG TTC CCT GAT GTC AAA GTC TAC GGC TCA GAT AAC ATC ACT AAA GAA ATT GTC GAT
 V   Q   E   M   F   P   D   V   K   V   Y   G   S   D   N   I   T   K   E   I   V   D>
```

0.52

Fig. 4

4/30

```
                6760                6780                6800
GAG AAC GTA CTT GCC GGT AAC GCC ATG AGC CGC CGC GCA GCT TAT CAA TAC GGC GCA ACA CTG GGC
 E   N   V   L   A   G   N   A   M   S   R   R   A   A   Y   Q   Y   G   A   T   L   G>

      6820                6840                6860
AAA CAT GAC CAC GGT ATT GTT GAT GCT GCG CTA GGT AAA GGT CTA TCA AAA GGT GAA ATC ACT TAC
 K   H   D   H   G   I   V   D   A   A   L   G   K   G   L   S   K   G   E   I   T   Y>

6880                6900                6920                6940
GTC GCC CCA GAC TAC ACC TTA AAC AGT GAA GGC AAA TGG GAA ACG CTG ACG ATT GAT GGT CTA GAG
 V   A   P   D   Y   T   L   N   S   E   G   K   W   E   T   L   T   I   D   G   L   E>

                6960                6980                7000
ATG GTG TTT ATG GAT GCC TCG GGC ACC GAA GCT GAG TCA GAA ATG ATC ACT TAT ATT CCC TCT AAA
 M   V   F   M   D   A   S   G   T   E   A   E   S   E   M   I   T   Y   I   P   S   K>

      7020                7040                7060
AAA GCG CTC TGG ACG GCG GAG CTT ACC TAT CAA GGT ATG CAC AAC ATT TAT ACG CTG CGC GGC GCT
 K   A   L   W   T   A   E   L   T   Y   Q   G   M   H   N   I   Y   T   L   R   G   A>

7080                7100                7120                7140
AAA GTA CGT GAT GCG CTC AAG TGG TCA AAA GAT ATC AAC GAA ATG ATC AAT GCC TTT GGT CAA GAT
 K   V   R   D   A   L   K   W   S   K   D   I   N   E   M   I   N   A   F   G   Q   D>

                7160                7180                7200
GTC GAA GTG CTG TTT GCC TCG CAC TCT GCG CCA GTG TGG GGT AAC CAA GCG ATC AAC GAT TTC TTA
 V   E   V   L   F   A   S   H   S   A   P   V   W   G   N   Q   A   I   N   D   F   L>

          7220                7240                7260
CGC CTA CAG CGT GAT AAC TAC GGC CTA GTG CAC AAT CAA ACC TTG AGA CTT GCC AAC GAT GGT GTC
 R   L   Q   R   D   N   Y   G   L   V   H   N   Q   T   L   R   L   A   N   D   G   V>

      7280                7300                7320                7340
GGT ATA CAA GAT ATT GGC GAT GCG ATT CAA GAC ACG ATT CCA GAG TCT ATC TAC AAG ACG TGG CAT
 G   I   Q   D   I   G   D   A   I   Q   D   T   I   P   E   S   I   Y   K   T   W   H>

                7360                7380                7400
ACC AAT GGT TAC CAC GGC ACT TAT AGC CAT AAC GCT AAA GCG GTT TAT AAC AAG TAT CTA GGC TAC
 T   N   G   Y   H   G   T   Y   S   H   N   A   K   A   V   Y   N   K   Y   L   G   Y>

          7420                7440                7460
TTC GAT ATG AAC CCA GCC AAC CTT AAT CCG CTG CCA ACC AAG CAA GAA TCT GCC AAG TTT GTC GAA
 F   D   M   N   P   A   N   L   N   P   L   P   T   K   Q   E   S   A   K   F   V   E>

      7480                7500                7520
TAC ATG GGC GGC GCA GAT GCC GCA ATT AAG CGC GCT AAA GAT GAT TAC GCT CAA GGT GAA TAC CGC
 Y   M   G   G   A   D   A   A   I   K   R   A   K   D   D   Y   A   Q   G   E   Y   R>

7540                7560                7580                7600
TTT GTT GCA ACG GCA TTA AAT AAG GTG GTG ATG GCC GAG CCA GAA AAT GAC TCC GCT CGT CAA TTG
 F   V   A   T   A   L   N   K   V   V   M   A   E   P   E   N   D   S   A   R   Q   L>

          7620                7640                7660
CTA GCC GAT ACC TAT GAG CAA CTT GGT TAT CAA GCA GAA GGG GCT GGC TGG AGA AAC ATT TAC TTA
 L   A   D   T   Y   E   Q   L   G   Y   Q   A   E   G   A   G   W   R   N   I   Y   L>

      7680                7700                7720
ACT GGC GCA CAA GAG CTA CGA GTA GGT ATT CAA GCT GGC GCG CCT AAA ACC GCA TCG GCA GAT GTC
 T   G   A   Q   E   L   R   V   G   I   Q   A   G   A   P   K   T   A   S   A   D   V>

7740                7760                7780                7800
ATC AGT GAA ATG GAC ATG CCG ACT CTA TTT GAC TTC CTC GCG GTG AAG ATT GAT AGT CAA CAG GCG
 I   S   E   M   D   M   P   T   L   F   D   F   L   A   V   K   I   D   S   Q   Q   A>

                7820                7840                7860
GCT AAG CAC GGC TTA GTT AAG ATG AAT GTT ATC ACC CCT GAT ACT AAA GAT ATT CTC TAT ATT GAG
 A   K   H   G   L   V   K   M   N   V   I   T   P   D   T   K   D   I   L   Y   I   E>

          7880                7900                7920
CTA AGC AAC GGT AAC TTA AGC AAC GCA GTG GTC GAC AAA GAG CAA GCA GCT GAC GCA AAC CTT ATG
 L   S   N   G   N   L   S   N   A   V   V   D   K   E   Q   A   A   D   A   N   L   M>
```

Fig. 4

5/30

```
7940                    7960                    7980                    8000
GTT AAT AAA GCT GAC GTT AAC CGC ATC TTA CTT GGC CAA GTA ACC CTA AAA GCG TTA TTA GCC AGC
 V   N   K   A   D   V   N   R   I   L   L   G   Q   V   T   L   K   A   L   L   A  S>

                8020                    8040                    8060
GGC GAT GCC AAG CTC ACT GGT GAT AAA ACG GCA TTT AGT AAA ATA GCC GAT AGC ATG GTC GAG TTT
 G   D   A   K   L   T   G   D   K   T   A   F   S   K   I   A   D   S   M   V   E  F>

        8080                    8100                    8120                    8140
ACA CCT GAC TTC GAA ATC GTA CCA ACG CCT GTT AAA TGAGGCA TTAATCTCAA CAAGTGCAAG CTAGACATAA
 T   P   D   F   E   I   V   P   T   P   V  K>

            8160                    8180                    8200
AAATGGGGCG ATTAGACGCC CCATTTTTTA TGCAATTTTG AACTA GCT AGT CTT AGC TGA AGC TCG AAC AAC
                                             <S   T   K   A   S   A   R   V   V

      8220                    8240                    8260
AGC TTT AAA ATT CAC TTC TTC TGC TGC AAT ACT TAT TTG CTG ACA CTG ACC AAT ACT CAG TGC AAA
<A   K   F   N   V   E   E   A   A   I   S   I   Q   Q   C   Q   G   I   S   L   A   F

8280                    8300                    8320                    8340
ACG ATA ACT ATC ATC AAG ATG GCC CAG TAA ACA ATG CCA ATT ATC AGC AGC GTT CAT TTG CTG TTC
<R   Y   S   D   D   L   H   G   L   L   C   H   W   N   D   A   A   N   M   Q   Q   E

            8360                    8380                    8400
TTT AGC CTC AAT CAA ACC TAA ACC AGA CTT TTG TGG CTC AGC GTT AGG CTT ATT AGA ACT CGA CTC
<K   A   E   I   L   G   L   G   S   K   Q   P   E   A   N   P   K   N   S   S   S   E

        8420                    8440                    8460
TAG TAA AGC AAG ACC AAT ATC TTG TTT TAA CAA AAC CTG TCG CTG ATT AAG TTG ATG CTC AAC CTT
<L   L   A   L   G   I   D   Q   K   L   L   V   Q   R   Q   N   L   Q   H   E   V   K

8480                    8500                    8520                    8540
GTG ATC CGC AAT AGC ATC GGA AAT ATC AAC ACA ATG GCT CAA GCT TTT AGG TGC ATT AAC TCC AAG
<H   D   A   I   A   D   S   I   D   V   C   H   S   L   S   K   P   A   N   V   G   L

            8560                    8580                    8600
AAA AGT TTC GCT CAG TGC AGA GAA GTC AAA CGC AAA AGA TTT TAG CGA TAA TGC CAG CCC AAG TCC
<F   T   E   S   L   A   S   F   D   F   A   F   S   K   L   S   L   A   L   G   L   G

        8620                    8640                    8660
TTT CGC TTT AAT GTA AGA CTC CTT GAG CGC CCA CAA ATC AAA AAA GCG GTC TCG CTG CAA GGC CTC
<K   A   K   I   Y   S   E   K   L   A   W   L   D   F   F   R   D   R   Q   L   A   E

    8680                    8700                    8720                    8740
TGG TAA CGC TAA CAA GGC TCG CTT TTC TGA TTC AGA GAA ATA ATG ACT AAG AAT AGA GTG GAT ATT
<P   L   A   L   L   A   R   K   E   S   E   S   F   Y   H   S   L   I   S   H   I   N

                8760                    8780                    8800
GGT GCT GTT ACG GCA ACG CTC AAT GTC GAC GCC AAA CTC AAT ACT AGC AGA GTC AGT TTC CTC CTT
<T   S   N   R   C   R   E   I   D   V   G   F   E   I   S   A   S   D   T   E   E   K

            8820                    8840                    8860
GCT TGC CTG ACT GGC GCC TTT ATT ATC AGC AGT GCA AAT GCC TAC TAA TAG CCA ATC TCC ACT ATG
<S   A   Q   S   A   G   K   N   D   A   T   C   I   G   V   L   L   W   D   G   S   H

      8880                    8900                    8920
ACT CAC ATT AAA GTG GAC CCC GGT TTG AGC AAA TTG CGC ATC ACT CAA TCT AGG CTT ACC TTT GTC
<S   V   N   F   H   V   G   T   Q   A   F   Q   A   D   S   L   R   P   K   G   K   D

8940                    8960                    8980                    9000
GCC ATA TTC AAA GCG CCA TTC ATT GGG GCG TAT TTC ACT ATG TTG TGA CAA TAA AGC GCG CAA ATA
<G   Y   E   F   R   W   E   N   P   R   I   E   S   H   Q   S   L   L   A   R   L   Y

                9020                    9040                    9060                    9080
GCC TCT TAC CAT TAAA CCTTGAGTTT TAGCTTCTTG TTTAATGTAG CGATTAACCT TAATTAACTC ATCTTCAGGC
<G   R   V   M

            9100                    9120                    9140                    9160
AGCCATGACT TAACCAACTC TGTAGTCTGG TTATCGCACT CTTGTATTGT TAACGGACAG AAGTATAAGG AAATCAATCG
```

0-43

Fig. 4

6/30

```
                9180                9200                9220                9240
AGAAGTTAGC AATTTTTCAG GACACTCTTT AAAGCAACAA ACATAACCCC TATTTTTACC AATTTAAGAT CAAAACTAAA

                9260                9280                9300                9320
GCCAAAACTA ATTGAGAATA GTGTCAAACT AGCTTTAAAG GAAAAAAATA TAAAAAGAAC ATTATACTTG TATAAATTAT

                9340                9360                9380                9400
TTTACACACC AAAGCCATGA TCTTCACAAA ATTAGCTCCC TCTCCCTAAA ACAAGATTGA ATAAAAAAAT AAACCTTAAC

                9420                9440                9460                9480
TTTCATATAG ATAAAACAAA CCAATGGGAT AAAGTATATT GAATTCATTT TTAAGGAAAA ATTCAAATTG AATTCAAGCT

                9500                9520                9540                9560
CTTCAGTAAA AGCATATTTT GCCGTTAGTG TGAAAAAAAA CAAATTTAAA AACCAACATA GAACAAATAA GCAGACAATA

                9580                9600                9620                9640
AAACCAAGGC GCAACACAAA CAACGCGCTT ACAATTTTCA CAAAAAAGCA ACAAGAGTAA CGTTTAGTAT TTGGATATGG

                9660                9680                9700
TTATTGTAAT TGAGAATTTT ATAACAATTA TATTAAGGGA ATG AGT ATG TTT TTA AAT TCA AAA CTT TCG CGC
                                            M   S   M   F   L   N   S   K   L   S   R>

      9720                9740                9760
TCA GTC AAA CTT GCC ATA TCC GCA GGC TTA ACA GCC TCG CTA GCT ATG CCT GTT TTT GCA GAA GAA
 S   V   K   L   A   I   S   A   G   L   T   A   S   L   A   M   P   V   F   A   E   E>

9780                9800                9820                9840
ACT GCT GCT GAA GAA CAA ATA GAA AGA GTC GCA GTG ACC GGA TCG CGA ATC GCT AAA GCA GAG CTA
 T   A   A   E   E   Q   I   E   R   V   A   V   T   G   S   R   I   A   K   A   E   L>

              9860                9880                9900
ACT CAA CCA GCT CCA GTC GTC AGC CTT TCA GCC GAA GAA CTG ACA AAA TTT GGT AAT CAA GAT TTA
 T   Q   P   A   P   V   V   S   L   S   A   E   E   L   T   K   F   G   N   Q   D   L>

       9920                9940                9960
GGT AGC GTA CTA GCA GAA TTA CCT GCT ATT GGT GCA ACC AAC ACT ATT ATT GGT AAT AAC AAT AGC
 G   S   V   L   A   E   L   P   A   I   G   A   T   N   T   I   I   G   N   N   N   S>

9980                10000               10020               10040
AAC TCA AGC GCA GGT GTT AGC TCA GCA GAC TTG CGT CGT CTA GGT GCT AAC AGA ACC TTA GTA TTA
 N   S   S   A   G   V   S   S   A   D   L   R   R   L   G   A   N   R   T   L   V   L>

              10060               10080               10100
GTC AAC GGT AAG CGC TAC GTT GCC GGC CAA CCG GGC TCA GCT GAG GTA GAT TTG TCA ACT ATA CCA
 V   N   G   K   R   Y   V   A   G   Q   P   G   S   A   E   V   D   L   S   T   I   P>

        10120               10140               10160
ACT AGC ATG ATC TCG CGA GTT GAG ATT GTA ACC GGC GGT GCT TCA GCA ATT TAT GGT TCG GAC GCT
 T   S   M   I   S   R   V   E   I   V   T   G   G   A   S   A   I   Y   G   S   D   A>

 10180               10200               10220               10240
GTA TCA GGT GTT ATC AAC GTT ATC CTT AAA GAA GAC TTT GAA GGC TTT GAG TTT AAC GCA CGT ACT
 V   S   G   V   I   N   V   I   L   K   E   D   F   E   G   F   E   F   N   A   R   T>

                10260               10280               10300
AGC GGT TCT ACT GAA AGT GTA GGC ACT CAA GAG CAC TCT TTT GAC ATT TTG GGT GGT GCA AAC GTT
 S   G   S   T   E   S   V   G   T   Q   E   H   S   F   D   I   L   G   G   A   N   V>

            10320               10340               10360
GCA GAT GGA CGT GGT AAT GTA ACC TTC TAC GCA GGT TAT GAA CGT ACA AAA GAA GTC ATG GCT ACC
 A   D   G   R   G   N   V   T   F   Y   A   G   Y   E   R   T   K   E   V   M   A   T>

     10380               10400               10420
GAC ATT CGC CAA TTC GAT GCT TGG GGA ACA ATT AAA AAC GAA GCC GAT GGT GGT GAA GAT GAT GGT
 D   I   R   Q   F   D   A   W   G   T   I   K   N   E   A   D   G   G   E   D   D   G>

10440               10460               10480               10500
ATT CCA GAC AGA CTA CGT GTA CCA CGA GTT TAT TCT GAA ATG ATT AAT GCT ACC GGT GTT ATC AAT
 I   P   D   R   L   R   V   P   R   V   Y   S   E   M   I   N   A   T   G   V   I   N>
```

Fig. 4

7/30

```
                10520                   10540                   10560
GCA TTT GGT GGT GGA ATT GGT CGC TCA ACC TTT GAC AGT AAC GGC AAT CCT ATT GCA CAA CAA GAA
 A   F   G   G   G   I   G   R   S   T   F   D   S   N   G   N   P   I   A   Q   Q   E>

      10580                   10600                   10620
CGT GAT GGG ACT AAC AGC TTT GCA TTT GGT TCA TTC CCT AAT GGC TGT GAC ACA TGT TTC AAC ACT
 R   D   G   T   N   S   F   A   F   G   S   F   P   N   G   C   D   T   C   F   N   T>

10640                   10660                   10680                   10700
GAA GCA TAC GAA AAC TAT ATT CCA GGG GTA GAA AGA ATA AAC GTT GGC TCA TCA TTC AAC TTT GAT
 E   A   Y   E   N   Y   I   P   G   V   E   R   I   N   V   G   S   S   F   N   F   D>

                10720                   10740                   10760
TTT ACC GAT AAC ATT CAA TTT TAC ACT GAC TTC AGA TAT GTA AAG TCA GAT ATT CAG CAA CAA TTT
 F   T   D   N   I   Q   F   Y   T   D   F   R   Y   V   K   S   D   I   Q   Q   Q   F>

        10780                   10800                   10820
CAG CCT TCA TTC CGT TTT GGT AAC ATT AAT ATC AAT GTT GAA GAT AAC GCC TTT TTG AAT GAC GAC
 Q   P   S   F   R   F   G   N   I   N   I   N   V   E   D   N   A   F   L   N   D   D>

10840                   10860                   10880                   10900
TTG CGT CAG CAA ATG CTC GAT GCG GGT CAA ACC AAT GCT AGT TTT GCC AAG TTT TTT GAT GAA TTA
 L   R   Q   Q   M   L   D   A   G   Q   T   N   A   S   F   A   K   F   F   D   E   L>

                10920                   10940                   10960
GGA AAT CGC TCA GCA GAA AAT AAA CGC GAA CTT TTC CGT TAC GTA GGT GGC TTT AAA GGT GGC TTT
 G   N   R   S   A   E   N   K   R   E   L   F   R   Y   V   G   G   F   K   G   G   F>

        10980                   11000                   11020
GAT ATT AGC GAA ACC ATA TTT GAT TAC GAC CTT TAC TAT GTT TAT GGC GAG ACT AAT AAC CGT CGT
 D   I   S   E   T   I   F   D   Y   D   L   Y   Y   V   Y   G   E   T   N   N   R   R>

      11040                   11060                   11080
AAA ACC CTT AAT GAC CTA ATT CCT GAT AAC TTT GTC GCA GCT GTC GAC TCT GTT ATT GAT CCT GAT
 K   T   L   N   D   L   I   P   D   N   F   V   A   A   V   D   S   V   I   D   P   D>

11100                   11120                   11140                   11160
ACT GGC TTA GCA GCG TGT CGC TCA CAA GTA GCA AGC GCT CAA GGC GAT GAC TAT ACA GAT CCC GCG
 T   G   L   A   A   C   R   S   Q   V   A   S   A   Q   G   D   D   Y   T   D   P   A>

                11180                   11200                   11220
TCT GTA AAT GGT AGC GAC TGT GTT GCT TAT AAC CCA TTT GGC ATG GGT CAA GCT TCA GCA GAA GCC
 S   V   N   G   S   D   C   V   A   Y   N   P   F   G   M   G   Q   A   S   A   E   A>

        11240                   11260                   11280
CGC GAC TGG GTT TCT GCT GAT GTG ACT CGT GAA GAC AAA ATA ACT CAA CAA GTG ATT GGT GGT ACT
 R   D   W   V   S   A   D   V   T   R   E   D   K   I   T   Q   Q   V   I   G   G   T>

11300                   11320                   11340                   11360
CTC GGT ACC GAT TCT GAA GAA CTA TTT GAG CTT CAA GGT GGT GCA ATC GCT ATG GTT GTT GGT TTT
 L   G   T   D   S   E   E   L   F   E   L   Q   G   G   A   I   A   M   V   V   G   F>

                11380                   11400                   11420
GAA TAC CGT GAA GAA ACG TCT GGT TCA ACA ACC GAT GAA TTT ACT AAA GCA GGT TTC TTG ACA AGC
 E   Y   R   E   E   T   S   G   S   T   T   D   E   F   T   K   A   G   F   L   T   S>

        11440                   11460                   11480
GCT GCA ACG CCA GAT TCT TAT GGC GAA TAC GAC GTG ACT GAG TAT TTT GTT GAG GTG AAC ATC CCA
 A   A   T   P   D   S   Y   G   E   Y   D   V   T   E   Y   F   V   E   V   N   I   P>

11500                   11520                   11540                   11560
GTA CTA AAA GAA TTA CCT TTT GCA CAT GAG TTG AGC TTT GAC GGT GCA TAC CGT AAT GCT GAT TAC
 V   L   K   E   L   P   F   A   H   E   L   S   F   D   G   A   Y   R   N   A   D   Y>

                11580                   11600                   11620
TCA CAT GCC GGT AAG ACT GAA GCA TGG AAA GCT GGT ATG TTC TAC TCA CCA TTA GAG CAA CTT GCA
 S   H   A   G   K   T   E   A   W   K   A   G   M   F   Y   S   P   L   E   Q   L   A>

        11640                   11660                   11680
TTA CGT GGT ACG GTA GGT GAA GCA GTA CGA GCA CCA AAC ATT GCA GAA GCC TTT AGT CCA CGC TCT
```

Fig. 4
8/30

```
  L  R  G  T  V  G  E  A  V  R  A  P  N  I  A  E  A  F  S  P  R  S>

     11700                 11720                 11740
CCT GGT TTT GGC CGC GTT TCA GAT CCA TGT GAT GCA GAT AAC ATT AAT GAC GAT CCG GAT CGC GTG
 P  G  F  G  R  V  S  D  P  C  D  A  D  N  I  N  D  D  P  D  R  V>

11760                 11780                 11800                 11820
TCA AAC TGT GCA GCA TTG GGG ATC CCT CCA GGA TTC CAA GCT AAT GAT AAC GTC AGT GTA GAT ACC
 S  N  C  A  A  L  G  I  P  P  G  F  Q  A  N  D  N  V  S  V  D  T>

           11840                 11860                 11880
TTA TCT GGT GGT AAC CCA GAT CTA AAA CCT GAA ACA TCA ACA TCC TTT ACA GGT GGT CTT GTT TGG
 L  S  G  G  N  P  D  L  K  P  E  T  S  T  S  F  T  G  G  L  V  W>

     11900                 11920                 11940
ACA CCA ACG TTT GCT GAC AAT CTA TCA TTC ACT GTC GAT TAT TAT GAT ATT CAA ATT GAG GAT GCT
 T  P  T  F  A  D  N  L  S  F  T  V  D  Y  Y  D  I  Q  I  E  D  A>

11960                 11980                 12000                 12020
ATT TTG TCA GTA GCC ACC CAG ACT GTG GCT GAT AAC TGT GTT GAC TCA ACT GGC GGA CCT GAC ACC
 I  L  S  V  A  T  Q  T  V  A  D  N  C  V  D  S  T  G  G  P  D  T>

           12040                 12060                 12080
GAC TTC TGT AGT CAA GTT GAT CGT AAT CCA ACG ACC TAT GAT ATT GAA CTT GTT CGC TCT GGT TAT
 D  F  C  S  Q  V  D  R  N  P  T  T  Y  D  I  E  L  V  R  S  G  Y>

     12100                 12120                 12140
CTA AAT GCC GCG GCA TTG AAT ACC AAA GGT ATT GAA TTT CAA GCT GCA TAC TCA TTA GAT CTA GAG
 L  N  A  A  A  L  N  T  K  G  I  E  F  Q  A  A  Y  S  L  D  L  E>

12160                 12180                 12200                 12220
TCT TTC AAC GCG CCT GGT GAA CTA CGC TTC AAC CTA TTG GGG AAC CAA TTA CTT GAA CTA GAA CGT
 S  F  N  A  P  G  E  L  R  F  N  L  L  G  N  Q  L  L  E  L  E  R>

           12240                 12260                 12280
CTT GAA TTC CAA AAT CGT CCT GAT GAG ATT AAT GAT GAA AAA GGC GAA GTA GGT GAT CCA GAG CTG
 L  E  F  Q  N  R  P  D  E  I  N  D  E  K  G  E  V  G  D  P  E  L>

     12300                 12320                 12340
CAG TTC CGC CTA GGC ATC GAT TAC CGT CTA GAT GAT CTA AGT GTT AGC TGG AAC ACG CGT TAT ATT
 Q  F  R  L  G  I  D  Y  R  L  D  D  L  S  V  S  W  N  T  R  Y  I>

     12360                 12380                 12400
GAT AGC GTA GTA ACT TAT GAT GTC TCT GAA AAT GGT GGC TCT CCT GAA GAT TTA TAT CCA GGC CAC
 D  S  V  V  T  Y  D  V  S  E  N  G  G  S  P  E  D  L  Y  P  G  H>

12420                 12440                 12460                 12480
ATA GGC TCA ATG ACA ACT CAT GAC TTG AGC GCT ACA TAC TAC ATC AAT GAG AAC TTC ATG ATT AAC
 I  G  S  M  T  T  H  D  L  S  A  T  Y  Y  I  N  E  N  F  M  I  N>

           12500                 12520                 12540
GGT GGT GTA CGT AAC CTA TTT GAC GCA CTT CCA CCT GGA TAC ACT AAC GAT GCG CTA TAT GAT CTA
 G  G  V  R  N  L  F  D  A  L  P  P  G  Y  T  N  D  A  L  Y  D  L>

     12560                 12580                 12600                 12620
GTT GGT CGC CGT GCA TTC CTA GGT ATT AAG GTA ATG ATG TAATTAATTA TTACGCCTCT AACTAATAAA
 V  G  R  R  A  F  L  G  I  K  V  M  M>

           12640                 12660                 12680                 12700
AATGCAATCT CTTCGTAGAG ATTGCATTTT TTTATGAAAT CCAATCTTAA ACTGGTTCTC CGAGCATCTT ACGCCTTAAA

           12720                 12740                 12760                 12780
AACCCCGCCC CTCAATGTAA CGCCAAAGTT AATTGCTTAC ACGCACTTAC ACAAACGAAC AATTTCATTA ACACGAGACA

           12800                 12820                 12840                 12860
CAGCTCACGC TTTTTATTTT ACCCTTGATT TTACTACATA AAATTGCGTT TTAGCGCACA AGTGTTCTCC CAAGCTGGTC

           12880                 12900                 12920                 12940
GTATCTGTAA TTATTCAGTC CCAGGTGATT GTATTGACCC ATAAGCTCAG GTAGTCTGCT CTGCCATTAG CTAAACAATA

           12960                 12980                 13000                 13020
```

look for Fur

Fig. 4

9/30

```
TTGACAAAAT GGCGATAAAA TGTGGCTTAG CGCTAAGTTC ACCGTAAGTT TTATCGGCAT TAAGTCCCAA CAGATTATTA

                13040                 13060                 13080
ACGGAAACCC GCTAAACTG ATG GCA AAA ATA AAT AGT GAA CAC TTG GAT GAA GCT ACT ATT ACT TCG AAT
                      M   A   K   I   N   S   E   H   L   D   E   A   T   I   T   S   N>

        13100                 13120                 13140
AAG TGT ACG CAA ACA GAG ACT GAG GCT CGG CAT AGA AAT GCC ACT ACA ACA CCT GAG ATG CGC CGA
 K   C   T   Q   T   E   T   E   A   R   H   R   N   A   T   T   T   P   E   M   R   R>

13160                 13180                 13200                 13220
TTC ATA CAA GAG TCG GAT CTC AGT GTT AGC CAA CTG TCT AAA ATA TTA AAT ATC AGT GAA GCT ACC
 F   I   Q   E   S   D   L   S   V   S   Q   L   S   K   I   L   N   I   S   E   A   T>

                13240                 13260                 13280
GTA CGT AAG TGG CGC AAG CGT GAC TCT GTC GAA AAC TGT CCT AAT ACC CCG CAC CAT CTC AAT ACC
 V   R   K   W   R   K   R   D   S   V   E   N   C   P   N   T   P   H   H   L   N   T>

        13300                 13320                 13340
ACG CTA ACC CCT TTG CAA GAA TAT GTG GTT GTG GGC CTG CGT TAT CAA TTG AAA ATG CCA TTA GAC
 T   L   T   P   L   Q   E   Y   V   V   V   G   L   R   Y   Q   L   K   M   P   L   D>

  13360                 13380                 13400                 13420
AGA TTG CTC AAA GCA ACC CAA GAG TTT ATC AAT CCA AAC GTG TCG CGC TCA GGT TTA GCA AGA TGT
 R   L   L   K   A   T   Q   E   F   I   N   P   N   V   S   R   S   G   L   A   R   C>

                13440                 13460                 13480
TTG AAG CGT TAT GGC GTT TCA CGG GTG AGT GAT ATC CAA AGC CCA CAC GTA CCA ATG CGC TAC TTT
 L   K   R   Y   G   V   S   R   V   S   D   I   Q   S   P   H   V   P   M   R   Y   F>

        13500                 13520                 13540
AAT CAA ATT CCA GTC ACT CAA GGC AGC GAT GTG CAA ACC TAC ACC CTG CAC TAT GAA ACG CTG GCA
 N   Q   I   P   V   T   Q   G   S   D   V   Q   T   Y   T   L   H   Y   E   T   L   A>

      13560                 13580                 13600
AAA ACC TTA GCC TTA CCT AGT ACC GAT GGT GAC AAT GTG GTG CAA GTG GTG TCT CTC ACC ATT CCA
 K   T   L   A   L   P   S   T   D   G   D   N   V   V   Q   V   V   S   L   T   I   P>

13620                 13640                 13660                 13680
CCA AAG TTA ACC GAA GAA GCA CCC AGT TCA ATT TTG CTC GGC ATT GAT CCT CAT AGC GAC TGG ATC
 P   K   L   T   E   E   A   P   S   S   I   L   L   G   I   D   P   H   S   D   W   I>

                13700                 13720                 13740
TAT CTC GAC ATA TAC CAA GAT GGC AAT ACA CAA GCC ACG AAT AGA TAT ATG GCT TAT GTG CTA AAA
 Y   L   D   I   Y   Q   D   G   N   T   Q   A   T   N   R   Y   M   A   Y   V   L   K>

        13760                 13780                 13800
CAC GGG CCA TTC CAT TTA CGA AAG TTA CTC GTG CGT AAC TAT CAC ACC TTT TTA CAG CGC TTT CCT
 H   G   P   F   H   L   R   K   L   L   V   R   N   Y   H   T   F   L   Q   R   F   P>

13820                 13840                 13860                 13880
GGA GCG ACG CAA AAT CGC CGC CCC TCT AAA GAT ATG CCT GAA ACA ATC AAC AAG ACG CCT GAA ACA
 G   A   T   Q   N   R   R   P   S   K   D   M   P   E   T   I   N   K   T   P   E   T>

                13900                 13920                 13940
CAG GCA CCC AGT GGA GAC TCA TA ATG AGC CAG ACC TCT AAA CCT ACA AAC TCA GCA ACT GAG CAA
 Q   A   P   S   G   D   S>
                          M   S   Q   T   S   K   P   T   N   S   A   T   E   Q>

        13960                 13980                 14000
GCA CAA GAC TCA CAA GCT GAC TCT CGT TTA AAT AAA CGA CTA AAA GAT ATG CCA ATT GCT ATT GTT
 A   Q   D   S   Q   A   D   S   R   L   N   K   R   L   K   D   M   P   I   A   I   V>

    14020                 14040                 14060
GGC ATG GCG AGT ATT TTT GCA AAC TCT CGC TAT TTG AAT AAG TTT TGG GAC TTA ATC AGC GAA AAA
 G   M   A   S   I   F   A   N   S   R   Y   L   N   K   F   W   D   L   I   S   E   K>

14080                 14100                 14120                 14140
ATT GAT GCG ATT ACT GAA TTA CCA TCA ACT CAC TGG CAG CCT GAA GAA TAT TAC GAC GCA GAT AAA
 I   D   A   I   T   E   L   P   S   T   H   W   Q   P   E   E   Y   Y   D   A   D   K>
```

Fig. 4

```
                                                
```

```
      15340                 15360                 15380
ACT AAC TTC CAT TTT GTA CTA GAA GAG TAC AAC CAA GAA CAC AGC CGT ACT GAT AGC GAA AAA GCT
 T   N   F   H   F   V   L   E   E   Y   N   Q   E   H   S   R   T   D   S   E   K   A>

15400                 15420                 15440                 15460
AAG TAT CGT CAA CGC CAA GTG GCG CAA AGC TTC CTT GTT AGC GCA AGC GAT AAA GCA TCG CTA ATT
 K   Y   R   Q   R   Q   V   A   Q   S   F   L   V   S   A   S   D   K   A   S   L   I>

          15480                 15500                 15520
AAC GAG TTA AAC GTA CTA GCA GCA TCT GCA AGC CAA GCT GAG TTT ATC CTC AAA GAT GCA GCA GCA
 N   E   L   N   V   L   A   A   S   A   S   Q   A   E   F   I   L   K   D   A   A   A>

      15540                 15560                 15580
AAC TAT GGC GTA CGT GAG CTT GAT AAA AAT GCA CCA CGG ATC GGT TTA GTT GCA AAC ACA GCT GAA
 N   Y   G   V   R   E   L   D   K   N   A   P   R   I   G   L   V   A   N   T   A   E>

15600                 15620                 15640                 15660
GAG TTA GCA GGC CTA ATT AAG CAA GCA CTT GCC AAA CTA GCA GCT AGC GAT GAT AAC GCA TGG CAG
 E   L   A   G   L   I   K   Q   A   L   A   K   L   A   A   S   D   D   N   A   W   Q>

              15680                 15700                 15720
CTA CCT GGT GGC ACT AGC TAC CGC GCC GCT GCA GTA GAA GGT AAA GTT GCC GCA CTG TTT GCT GGC
 L   P   G   G   T   S   Y   R   A   A   A   V   E   G   K   V   A   A   L   F   A   G>

          15740                 15760                 15780
CAA GGT TCA CAA TAT CTC AAT ATG GGC CGT GAC CTT ACT TGT TAT TAC CCA GAG ATG CGT CAG CAA
 Q   G   S   Q   Y   L   N   M   G   R   D   L   T   C   Y   Y   P   E   M   R   Q   Q>

 15800                 15820                 15840                 15860
TTT GTA ACT GCA GAT AAA GTA TTT GCC GCA AAT GAT AAA ACG CCG TTA TCG CAA ACT CTG TAT CCA
 F   V   T   A   D   K   V   F   A   A   N   D   K   T   P   L   S   Q   T   L   Y   P>

                  15880                 15900                 15920
AAG CCT GTA TTT AAT AAA GAT GAA TTA AAG GCT CAA GAA GCC ATT TTG ACC AAT ACC GCC AAT GCC
 K   P   V   F   N   K   D   E   L   K   A   Q   E   A   I   L   T   N   T   A   N   A>

          15940                 15960                 15980
CAA AGC GCA ATT GGT GCG ATT TCA ATG GGT CAA TAC GAT TTG TTT ACT GCG GCT GGC TTT AAT GCC
 Q   S   A   I   G   A   I   S   M   G   Q   Y   D   L   F   T   A   A   G   F   N   A>

    16000                 16020                 16040
GAC ATG GTT GCA GGC CAT AGC TTT GGT GAG CTA AGT GCA CTG TGT GCT GCA GGT GTT ATT TCA GCT
 D   M   V   A   G   H   S   F   G   E   L   S   A   L   C   A   A   G   V   I   S   A>

16060                 16080                 16100                 16120
GAT GAC TAC TAC AAG CTG GCT TTT GCT CGT GGT GAG GCT ATG GCA ACA AAA GCA CCG GCT AAA GAC
 D   D   Y   Y   K   L   A   F   A   R   G   E   A   M   A   T   K   A   P   A   K   D>

              16140                 16160                 16180
GGC GTT GAA GCA GAT GCA GGA GCA ATG TTT GCA ATC ATA ACC AAG AGT GCT GCA GAC CTT GAA ACC
 G   V   E   A   D   A   G   A   M   F   A   I   I   T   K   S   A   A   D   L   E   T>

        16200                 16220                 16240
GTT GAA GCC ACC ATC GCT AAA TTT GAT GGG GTG AAA GTC GCT AAC TAT AAC GCG CCA ACG CAA TCA
 V   E   A   T   I   A   K   F   D   G   V   K   V   A   N   Y   N   A   P   T   Q   S>

16260                 16280                 16300                 16320
GTA ATT GCA GGC CCA ACA GCA ACT ACC GCT GAT GCG GCT AAA GCG CTA ACT GAG CTT GGT TAC AAA
 V   I   A   G   P   T   A   T   T   A   D   A   A   K   A   L   T   E   L   G   Y   K>

                  16340                 16360                 16380
GCG ATT AAC CTG CCA GTA TCA GGT GCA TTC CAC ACT GAA CTT GTT GGT CAC GCT CAA GCG CCA TTT
 A   I   N   L   P   V   S   G   A   F   H   T   E   L   V   G   H   A   Q   A   P   F>

          16400                 16420                 16440
GCT AAA GCG ATT GAC GCA GCC AAA TTT ACT AAA ACA AGC CGA GCA CTT TAC TCA AAT GCA ACT GGC
 A   K   A   I   D   A   A   K   F   T   K   T   S   R   A   L   Y   S   N   A   T   G>

 16460                 16480                 16500                 16520
GGA CTT TAT GAA AGC ACT GCT GCA AAG ATT AAA GCC TCG TTT AAG AAA CAT ATG CTT CAA TCA GTG
```

Fig. 4
12/30

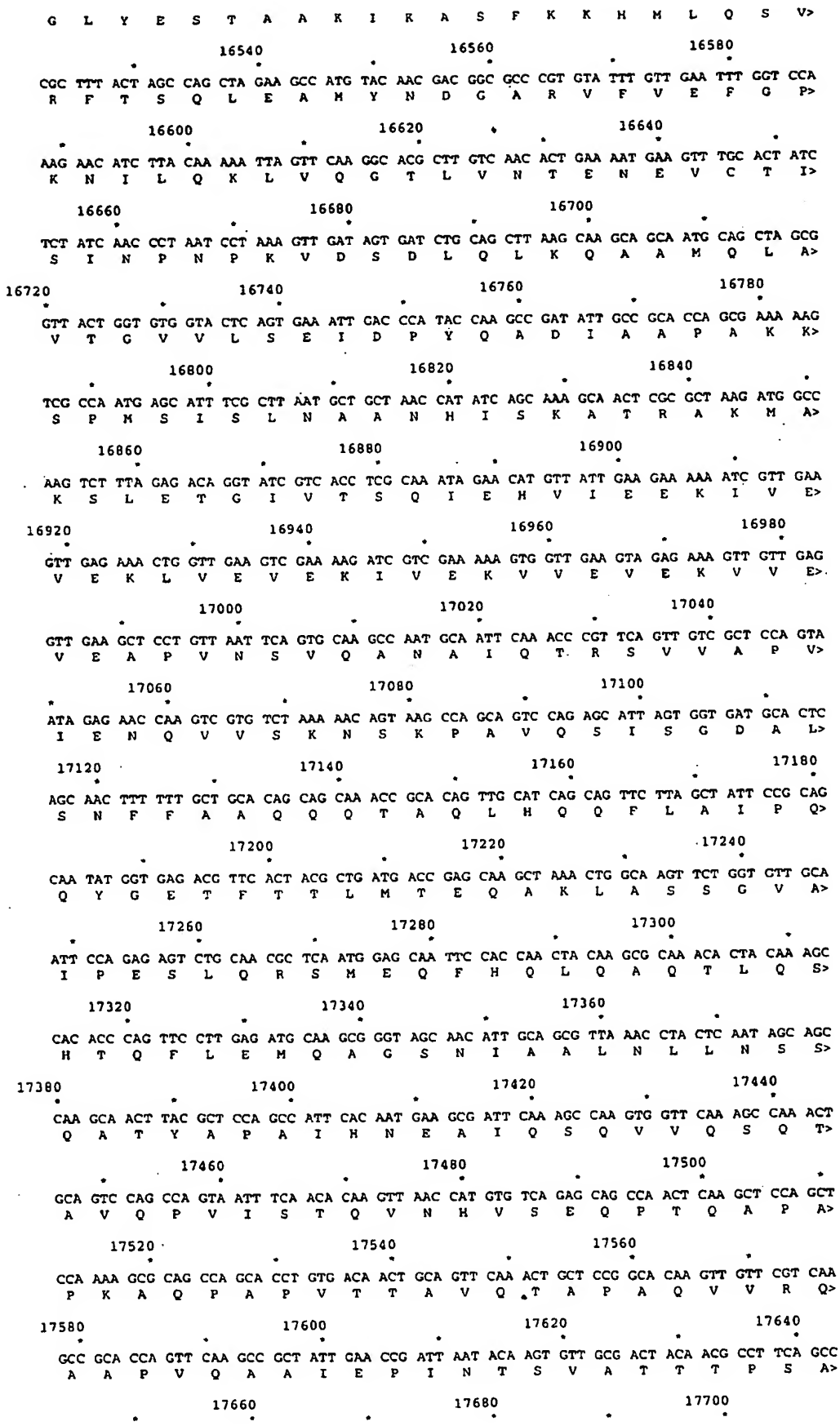

G L Y E S T A A K I K A S F K K H M L Q S V>
16540 16560 16580
CGC TTT ACT AGC CAG CTA GAA GCC ATG TAC AAC GAC GGC GCC CGT GTA TTT GTT GAA TTT GGT CCA
R F T S Q L E A M Y N D G A R V F V E F G P>
16600 16620 16640
AAG AAC ATC TTA CAA AAA TTA GTT CAA GGC ACG CTT GTC AAC ACT GAA AAT GAA GTT TGC ACT ATC
K N I L Q K L V Q G T L V N T E N E V C T I>
16660 16680 16700
TCT ATC AAC CCT AAT CCT AAA GTT GAT AGT GAT CTG CAG CTT AAG CAA GCA GCA ATG CAG CTA GCG
S I N P N P K V D S D L Q L K Q A A M Q L A>
16720 16740 16760 16780
GTT ACT GGT GTG GTA CTC AGT GAA ATT GAC CCA TAC CAA GCC GAT ATT GCC GCA CCA GCG AAA AAG
V T G V V L S E I D P Y Q A D I A A P A K K>
16800 16820 16840
TCG CCA ATG AGC ATT TCG CTT AAT GCT GCT AAC CAT ATC AGC AAA GCA ACT CGC GCT AAG ATG GCC
S P M S I S L N A A N H I S K A T R A K M A>
16860 16880 16900
AAG TCT TTA GAG ACA GGT ATC GTC ACC TCG CAA ATA GAA CAT GTT ATT GAA GAA AAA ATC GTT GAA
K S L E T G I V T S Q I E H V I E E K I V E>
16920 16940 16960 16980
GTT GAG AAA CTG GTT GAA GTC GAA AAG ATC GTC GAA AAA GTG GTT GAA GTA GAG AAA GTT GTT GAG
V E K L V E V E K I V E K V V E V E K V V E>
17000 17020 17040
GTT GAA GCT CCT GTT AAT TCA GTG CAA GCC AAT GCA ATT CAA ACC CGT TCA GTT GTC GCT CCA GTA
V E A P V N S V Q A N A I Q T R S V V A P V>
17060 17080 17100
ATA GAG AAC CAA GTC GTG TCT AAA AAC AGT AAG CCA GCA GTC CAG AGC ATT AGT GGT GAT GCA CTC
I E N Q V V S K N S K P A V Q S I S G D A L>
17120 17140 17160 17180
AGC AAC TTT TTT GCT GCA CAG CAG CAA ACC GCA CAG TTG CAT CAG CAG TTC TTA GCT ATT CCG CAG
S N F F A A Q Q Q T A Q L H Q Q F L A I P Q>
17200 17220 17240
CAA TAT GGT GAG ACG TTC ACT ACG CTG ATG ACC GAG CAA GCT AAA CTG GCA AGT TCT GGT GTT GCA
Q Y G E T F T T L M T E Q A K L A S S G V A>
17260 17280 17300
ATT CCA GAG AGT CTG CAA CGC TCA ATG GAG CAA TTC CAC CAA CTA CAA GCG CAA ACA CTA CAA AGC
I P E S L Q R S M E Q F H Q L Q A Q T L Q S>
17320 17340 17360
CAC ACC CAG TTC CTT GAG ATG CAA GCG GGT AGC AAC ATT GCA GCG TTA AAC CTA CTC AAT AGC AGC
H T Q F L E M Q A G S N I A A L N L L N S S>
17380 17400 17420 17440
CAA GCA ACT TAC GCT CCA GCC ATT CAC AAT GAA GCG ATT CAA AGC CAA GTG GTT CAA AGC CAA ACT
Q A T Y A P A I H N E A I Q S Q V V Q S Q T>
17460 17480 17500
GCA GTC CAG CCA GTA ATT TCA ACA CAA GTT AAC CAT GTG TCA GAG CAG CCA ACT CAA GCT CCA GCT
A V Q P V I S T Q V N H V S E Q P T Q A P A>
17520 17540 17560
CCA AAA GCG CAG CCA GCA CCT GTG ACA ACT GCA GTT CAA ACT GCT CCG GCA CAA GTT GTT CGT CAA
P K A Q P A P V T T A V Q T A P A Q V V R Q>
17580 17600 17620 17640
GCC GCA CCA GTT CAA GCC GCT ATT GAA CCG ATT AAT ACA AGT GTT GCG ACT ACA ACG CCT TCA GCC
A A P V Q A A I E P I N T S V A T T T P S A>
17660 17680 17700

Fig. 4

13/30

```
TTC AGC GCC GAA ACA GCC CTG AGC GCA ACA AAA GTC CAA GCC ACT ATG CTT GAA GTG GTT GCT GAG
 F  S  A  E  T  A  L  S  A  T  K  V  Q  A  T  M  L  E  V  V  A  E>

        17720                 17740                 17760
AAA ACC GGT TAC CCA ACT GAA ATG CTA GAG CTT GAA ATG GAT ATG GAA GCC GAT TTA GGC ATC GAT
 K  T  G  Y  P  T  E  M  L  E  L  E  M  D  M  E  A  D  L  G  I  D>

17780                 17800                 17820                 17840
TCT ATC AAG CGT GTA GAA ATT CTT GGC ACA GTA CAA GAT GAG CTA CCG GGT CTA CCT GAG CTT AGC
 S  I  K  R  V  E  I  L  G  T  V  Q  D  E  L  P  G  L  P  E  L  S>

                17860                 17880                 17900
CCT GAA GAT CTA GCT GAG TGT CGA ACG CTA GGC GAA ATC GTT GAC TAT ATG GGC AGT AAA CTG CCG
 P  E  D  L  A  E  C  R  T  L  G  E  I  V  D  Y  M  G  S  K  L  P>

          17920                 17940                 17960
GCT GAA GGC TCT ATG AAT TCT CAG CTG TCT ACA GGT TCC GCA GCT GCG ACT CCT GCA GCG AAT GGT
 A  E  G  S  M  N  S  Q  L  S  T  G  S  A  A  A  T  P  A  A  N  G>

    17980                 18000                 18020
CTT TCT GCG GAG AAA GTT CAA GCG ACT ATG ATG TCT GTG GTT GCC GAA AAG ACT GGC TAC CCA ACT
 L  S  A  E  K  V  Q  A  T  M  M  S  V  V  A  E  K  T  G  Y  P  T>

18040                 18060                 18080                 18100
GAA ATG CTA GAG CTT GAA ATG GAT ATG GAA GCC GAT TTA GGC ATA GAT TCT ATC AAG CGC GTT GAA
 E  M  L  E  L  E  M  D  M  E  A  D  L  G  I  D  S  I  K  R  V  E>

          18120                 18140                 18160
ATT CTT GGC ACA GTA CAA GAT GAG CTA CCG GGT CTA CCT GAG CTT AGC CCT GAA GAT CTA GCT GAG
 I  L  G  T  V  Q  D  E  L  P  G  L  P  E  L  S  P  E  D  L  A  E>

       18180                 18200                 18220
TGT CGT ACT CTA GGC GAA ATC GTT GAC TAT ATG AAC TCT AAA CTC GCT GAC GGC TCT AAG CTG CCG
 C  R  T  L  G  E  I  V  D  Y  M  N  S  K  L  A  D  G  S  K  L  P>

18240                 18260                 18280                 18300
GCT GAA GGC TCT ATG AAT TCT CAG CTG TCT ACA AGT GCC GCA GCT GCG ACT CCT GCA GCG AAT GGT
 A  E  G  S  M  N  S  Q  L  S  T  S  A  A  A  A  T  P  A  A  N  G>

                18320                 18340                 18360
CTC TCT GCG GAG AAA GTT CAA GCG ACT ATG ATG TCT GTG GTT GCC GAA AAG ACT GGC TAC CCA ACT
 L  S  A  E  K  V  Q  A  T  M  M  S  V  V  A  E  K  T  G  Y  P  T>

        18380                 18400                 18420
GAA ATG CTA GAA CTT GAA ATG GAT ATG GAA GCT GAC CTT GGC ATC GAT TCA ATC AAG CGC GTT GAA
 E  M  L  E  L  E  M  D  M  E  A  D  L  G  I  D  S  I  K  R  V  E>

 18440                 18460                 18480                 18500
ATT CTT GGC ACA GTA CAA GAT GAG CTA CCG GGT TTA CCT GAG CTA AAT CCA GAA GAT TTG GCA GAG
 I  L  G  T  V  Q  D  E  L  P  G  L  P  E  L  N  P  E  D  L  A  E>

                18520                 18540                 18560
TGT CGT ACT CTT GGC GAA ATC GTG ACT TAT ATG AAC TCT AAA CTC GCT GAC GGC TCT AAG CTG CCA
 C  R  T  L  G  E  I  V  T  Y  M  N  S  K  L  A  D  G  S  K  L  P>

          18580                 18600                 18620
GCT GAA GGC TCT ATG CAC TAT CAG CTG TCT ACA AGT ACC GCT GCT GCG ACT CCT GTA GCG AAT GGT
 A  E  G  S  M  H  Y  Q  L  S  T  S  T  A  A  A  T  P  V  A  N  G>

    18640                 18660                 18680
CTC TCT GCA GAA AAA GTT CAA GCG ACC ATG ATG TCT GTA GTT GCA GAT AAA ACT GGC TAC CCA ACT
 L  S  A  E  K  V  Q  A  T  M  M  S  V  V  A  D  K  T  G  Y  P  T>

18700                 18720                 18740                 18760
GAA ATG CTT GAA CTT GAA ATG GAT ATG GAA GCC GAT TTA GGT ATC GAT TCT ATC AAG CGC GTT GAA
 E  M  L  E  L  E  M  D  M  E  A  D  L  G  I  D  S  I  K  R  V  E>

                18780                 18800                 18820
ATT CTT GGC ACA GTA CAA GAT GAG CTA CCG GGT TTA CCT GAG CTA AAT CCA GAA GAT CTA GCA GAG
 I  L  G  T  V  Q  D  E  L  P  G  L  P  E  L  N  P  E  D  L  A  E>

       18840                 18860                 18880
```

Fig. 4
14/430

MISSING AT THE TIME OF PUBLICATION

```
20020                20040                20060                20080
GTT AGC AAT GCG TTC TTG TGG GCC AAA TTA TTG CAA CCA AAG CTC GTT GCT GGA GCA GAT GCG CGT
 V   S   N   A   F   L   W   A   K   L   L   Q   P   K   L   V   A   G   A   D   A   R>

          20100                20120                20140
CGC TGT TTT GTA ACA GTA AGC CGT ATC GAC GGT GGC TTT GGT TAC CTA AAT ACT GAC GCC CTA AAA
 R   C   F   V   T   V   S   R   I   D   G   G   F   G   Y   L   N   T   D   A   L   K>

     20160                20180                20200
GAT GCT GAG CTA AAC CAA GCA GCA TTA GCT GGT TTA ACT AAA ACC TTA AGC CAT GAA TGG CCA CAA
 D   A   E   L   N   Q   A   A   L   A   G   L   T   K   T   L   S   H   E   W   P   Q>

20220                20240                20260                20280
GTG TTC TGT CGC GCG CTA GAT ATT GCA ACA GAT GTT GAT GCA ACC CAT CTT GCT GAT GCA ATC ACC
 V   F   C   R   A   L   D   I   A   T   D   V   D   A   T   H   L   A   D   A   I   T>

          20300                20320                20340
AGT GAA CTA TTT GAT AGC CAA GCT CAG CTA CCT GAA GTG GGC TTA AGC TTA ATT GAT GGC AAA GTT
 S   E   L   F   D   S   Q   A   Q   L   P   E   V   G   L   S   L   I   D   G   K   V>

     20360                20380                20400
AAC CGC GTA ACT CTA GTT GCT GCT GAA GCT GCA GAT AAA ACA GCA AAA GCA GAG CTT AAC AGC ACA
 N   R   V   T   L   V   A   A   E   A   A   D   K   T   A   K   A   E   L   N   S   T>

20420                20440                20460                20480
GAT AAA ATC TTA GTG ACT GGT GGG GCA AAA GGG GTG ACA TTT GAA TGT GCA CTG GCA TTA GCA TCT
 D   K   I   L   V   T   G   G   A   K   G   V   T   F   E   C   A   L   A   L   A   S>

               20500                20520                20540
CGC AGC CAG TCT CAC TTT ATC TTA GCT GGG CGC AGT GAA TTA CAA GCT TTA CCA AGC TGG GCT GAG
 R   S   Q   S   H   F   I   L   A   G   R   S   E   L   Q   A   L   P   S   W   A   E>

          20560                20580                20600
GGT AAG CAA ACT AGC GAG CTA AAA TCA GCT GCA ATC GCA CAT ATT ATT TCT ACT GGT CAA AAG CCA
 G   K   Q   T   S   E   L   K   S   A   A   I   A   H   I   I   S   T   G   Q   K   P>

     20620                20640                20660
ACG CCT AAG CAA GTT GAA GCC GCT GTG TGG CCA GTG CAA AGC AGC ATT GAA ATT AAT GCC GCC CTA
 T   P   K   Q   V   E   A   A   V   W   P   V   Q   S   S   I   E   I   N   A   A   L>

20680                20700                20720                20740
GCC GCC TTT AAC AAA GTT GGC GCC TCA GCT GAA TAC GTC AGC ATG GAT GTT ACC GAT AGC GCC GCA
 A   A   F   N   K   V   G   A   S   A   E   Y   V   S   M   D   V   T   D   S   A   A>

          20760                20780                20800
ATC ACA GCA GCA CTT AAT GGT CGC TCA AAT GAG ATC ACC GGT CTT ATT CAT GGC GCA GGT GTA CTA
 I   T   A   A   L   N   G   R   S   N   E   I   T   G   L   I   H   G   A   G   V   L>

     20820                20840                20860
GCC GAC AAG CAT ATT CAA GAC AAG ACT CTT GCT GAA CTT GCT AAA GTT TAT GGC ACT AAA GTC AAC
 A   D   K   H   I   Q   D   K   T   L   A   E   L   A   K   V   Y   G   T   K   V   N>

20880                20900                20920                20940
GGC CTA AAA GCG CTG CTC GCG GCA CTT GAG CCA AGC AAA ATT AAA TTA CTT GCT ATG TTC TCA TCT
 G   L   K   A   L   L   A   A   L   E   P   S   K   I   K   L   L   A   M   F   S   S>

               20960                20980                21000
GCA GCA GGT TTT TAC GGT AAT ATC GGC CAA AGC GAT TAC GCG ATG TCG AAC GAT ATT CTT AAC AAG
 A   A   G   F   Y   G   N   I   G   Q   S   D   Y   A   M   S   N   D   I   L   N   K>

          21020                21040                21060
GCA GCG CTG CAG TTC ACC GCT CGC AAC CCA CAA GCT AAA GTC ATG AGC TTT AAC TGG GGT CCT TGG
 A   A   L   Q   F   T   A   R   N   P   Q   A   K   V   M   S   F   N   W   G   P   W>

21080                21100                21120                21140
GAT GGC GGC ATG GTT AAC CCA GCG CTT AAA AAG ATG TTT ACC GAG CGT GGT GTG TAC GTT ATT CCA
 D   G   G   M   V   N   P   A   L   K   K   M   F   T   E   R   G   V   Y   V   I   P>

               21160                21180                21200
CTA AAA GCA GGT GCA GAG CTA TTT GCC ACT CAG CTA TTG GCT GAA ACT GGC GTG CAG TTG CTC ATT
 L   K   A   G   A   E   L   F   A   T   Q   L   L   A   E   T   G   V   Q   L   L   I>
```

Fig. 4

16/30

```
                21220                 21240                 21260
GGT ACG TCA ATG CAA GGT GGC AGC GAC ACT AAA GCA ACT GAG ACT GCT TCT GTA AAA AAG CTT AAT
 G   T   S   M   Q   G   G   S   D   T   K   A   T   E   T   A   S   V   K   K   L   N>

    21280                 21300                 21320
GCG GGT GAG GTG CTA AGT GCA TCG CAT CCG CGT GCT GGT GCA CAA AAA ACA CCA CTA CAA GCT GTC
 A   G   E   V   L   S   A   S   H   P   R   A   G   A   Q   K   T   P   L   Q   A   V>

21340                 21360                 21380                 21400
ACT GCA ACG CGT CTG TTA ACC CCA AGT GCC ATG GTC TTC ATT GAA GAT CAC CGC ATT GGC GGT AAC
 T   A   T   R   L   L   T   P   S   A   M   V   F   I   E   D   H   R   I   G   G   N>

                21420                 21440                 21460
AGT GTG TTG CCA ACG GTA TGC GCC ATC GAC TGG ATG CGT GAA GCG GCA AGC GAC ATG CTT GGC GCT
 S   V   L   P   T   V   C   A   I   D   W   M   R   E   A   A   S   D   M   L   G   A>

    21480                 21500                 21520
CAA GTT AAG GTA CTT GAT TAC AAG CTA TTA AAA GGC ATT GTA TTT GAG ACT GAT GAG CCG CAA GAG
 Q   V   K   V   L   D   Y   K   L   L   K   G   I   V   F   E   T   D   E   P   Q   E>

21540                 21560                 21580                 21600
TTA ACA CTT GAG CTA ACG CCA GAC GAT TCA GAC GAA GCT ACG CTA CAA GCA TTA ATC AGC TGT AAT
 L   T   L   E   L   T   P   D   D   S   D   E   A   T   L   Q   A   L   I   S   C   N>

                21620                 21640                 21660
GGG CGT CCG CAA TAC AAG GCG ACG CTT ATC AGT GAT AAT GCC GAT ATT AAG CAA CTT AAC AAG CAG
 G   R   P   Q   Y   K   A   T   L   I   S   D   N   A   D   I   K   Q   L   N   K   Q>

        21680                 21700                 21720
TTT GAT TTA AGC GCT AAG GCG ATT ACC ACA GCA AAA GAG CTT TAT AGC AAC GGC ACC TTG TTC CAC
 F   D   L   S   A   K   A   I   T   T   A   K   E   L   Y   S   N   G   T   L   F   H>

    21740                 21760                 21780                 21800
GGT CCG CGT CTA CAA GGG ATC CAA TCT GTA GTG CAG TTC GAT GAT CAA GGC TTA ATT GCT AAA GTC
 G   P   R   L   Q   G   I   Q   S   V   V   Q   F   D   D   Q   G   L   I   A   K   V>

                21820                 21840                 21860
GCT CTG CCT AAG GTT GAA CTT AGC GAT TGT GGT GAG TTC TTG CCG CAA ACC CAC ATG GGT GGC AGT
 A   L   P   K   V   E   L   S   D   C   G   E   F   L   P   Q   T   H   M   G   G   S>

            21880                 21900                 21920
CAA CCT TTT GCT GAG GAC TTG CTA TTA CAA GCT ATG CTG GTT TGG GCT CGC CTT AAA ACT GGC TCG
 Q   P   F   A   E   D   L   L   L   Q   A   M   L   V   W   A   R   L   K   T   G   S>

    21940                 21960                 21980
GCA AGT TTG CCA TCA AGC ATT GGT GAG TTT ACC TCA TAC CAA CCA ATG GCC TTT GGT GAA ACT GGT
 A   S   L   P   S   S   I   G   E   F   T   S   Y   Q   P   M   A   F   G   E   T   G>

22000                 22020                 22040                 22060
ACC ATA GAG CTT GAA GTG ATT AAG CAC AAC AAA CGC TCA CTT GAA GCG AAT GTT GCG CTA TAT CGT
 T   I   E   L   E   V   I   K   H   N   K   R   S   L   E   A   N   V   A   L   Y   R>

            22080                 22100                 22120
GAC AAC GGC GAG TTA AGT GCC ATG TTT AAG TCA GCT AAA ATC ACC ATT AGC AAA AGC TTA AAT TCA
 D   N   G   E   L   S   A   M   F   K   S   A   K   I   T   I   S   K   S   L   N   S>

    22140                 22160                 22180                 22200
GCA TTT TTA CCT GCT GTC TTA GCA AAC GAC AGT GAG GCG AAT TAGTGGA ACAAACGCCT AAAGCTAGTG
 A   F   L   P   A   V   L   A   N   D   S   E   A   N>

                22220                 22240                 22260
CG ATG CCG CTG CGC ATC GCA CTT ATC TTA CTG CCA ACA CCG CAG TTT GAA GTT AAC TCT GTC GAC
   M   P   L   R   I   A   L   I   L   L   P   T   P   Q   F   E   V   N   S   V   D>

            22280                 22300                 22320
CAG TCA GTA TTA GCC AGC TAT CAA ACA CTG CAG CCT GAG CTA AAT GCC CTG CTT AAT AGT GCG CCG
 Q   S   V   L   A   S   Y   Q   T   L   Q   P   E   L   N   A   L   L   N   S   A   P>

    22340                 22360                 22380
ACA CCT GAA ATG CTC AGC ATC ACT ATC TCA GAT GAT AGC GAT GCA AAC AGC TTT GAG TCG CAG CTA
```

```
   T  P  E  M  L  S  I  T  I  S  D  D  S  D  A  N  S  F  E  S  Q  L>

22400                    22420                    22440                    22460
  .        .        .        .        .        .        .        .
  AAT GCT GCG ACC AAC GCA ATT AAC AAT GGC TAT ATC GTC AAG CTT GCT ACG GCA ACT CAC GCT TTG
   N  A  A  T  N  A  I  N  N  G  Y  I  V  K  L  A  T  A  T  H  A  L>

                22480                    22500                    22520
              .        .        .        .        .        .        .
  TTA ATG CTG CCT GCA TTA AAA GCG GCG CAA ATG CGG ATC CAT CCT CAT GCG CAG CTT GCC GCT ATG
   L  M  L  P  A  L  K  A  A  Q  M  R  I  H  P  H  A  Q  L  A  A  M>

          22540                    22560                    22580
  .        .        .        .        .        .        .        .
  CAG CAA GCT AAA TCG ACG CCA ATG AGT CAA GTA TCT GGT GAG CTA AAG CTT GGC GCT AAT GCG CTA
   Q  Q  A  K  S  T  P  M  S  Q  V  S  G  E  L  K  L  G  A  N  A  L>

  22600                    22620                    22640                    22660
    .        .        .        .        .        .        .        .
  AGC CTA GCT CAG ACT AAT GCG CTG TCT CAT GCT TTA AGC CAA GCC AAG CGT AAC TTA ACT GAT GTC
   S  L  A  Q  T  N  A  L  S  H  A  L  S  Q  A  K  R  N  L  T  D  V>

                22680                    22700                    22720
              .        .        .        .        .        .        .
  AGC GTG AAT GAG TGT TTT GAG AAC CTC AAA AGT GAA CAG CAG TTC ACA GAG GTT TAT TCG CTT ATT
   S  V  N  E  C  F  E  N  L  K  S  E  Q  Q  F  T  E  V  Y  S  L  I>

          22740                    22760                    22780
  .        .        .        .        .        .        .        .
  CAG CAA CTT GCT AGC CGC ACC CAT GTG AGA AAA GAG GTT AAT CAA GGT GTG GAA CTT GGC CCT AAA
   Q  Q  L  A  S  R  T  H  V  R  K  E  V  N  Q  G  V  E  L  G  P  K>

     22800                    22820                    22840
       .        .        .        .        .        .        .
  CAA GCC AAA AGC CAC TAT TGG TTT AGC GAA TTT CAC CAA AAC CGT GTT GCT GCC ATC AAC TTT ATT
   Q  A  K  S  H  Y  W  F  S  E  F  H  Q  N  R  V  A  A  I  N  F  I>

22860                    22880                    22900                    22920
  .        .        .        .        .        .        .        .
  AAT GGC CAA CAA GCA ACC AGC TAT GTG CTT ACT CAA GGT TCA GGA TTG TTA GCT GCG AAA TCA ATG
   N  G  Q  Q  A  T  S  Y  V  L  T  Q  G  S  G  L  L  A  A  K  S  M>

          22940                    22960                    22980
  .        .        .        .        .        .        .        .
  CTA AAC CAG CAA AGA TTA ATG TTT ATC TTG CCG GGT AAC AGT CAG CAA CAA ATA ACC GCA TCA ATA
   L  N  Q  Q  R  L  M  F  I  L  P  G  N  S  Q  Q  Q  I  T  A  S  I>

        23000                    23020                    23040
          .        .        .        .        .        .        .
  ACT CAG TTA ATG CAG CAA TTA GAG CGT TTG CAG GTA ACT GAG GTT AAT GAG CTT TCT CTA GAA TGC
   T  Q  L  M  Q  Q  L  E  R  L  Q  V  T  E  V  N  E  L  S  L  E  C>

23060                    23080                    23100                    23120
  .        .        .        .        .        .        .        .
  CAA CTA GAG CTG CTC AGC ATA ATG TAT GAC AAC TTA GTC AAC GCA GAC AAA CTC ACT ACT CGC GAT
   Q  L  E  L  L  S  I  M  Y  D  N  L  V  N  A  D  K  L  T  T  R  D>

                23140                    23160                    23180
              .        .        .        .        .        .        .
  AGT AAG CCC GCT TAT CAG GCT GTG ATT CAA GCA AGC TCT GTT AGC GCT GCA AAG CAA GAG TTA AGC
   S  K  P  A  Y  Q  A  V  I  Q  A  S  S  V  S  A  A  K  Q  E  L  S>

          23200                    23220                    23240
  .        .        .        .        .        .        .        .
  GCG CTT AAC GAT GCA CTC ACA GCG CTG TTT GCT GAG CAA ACA AAC GCC ACA TCA ACG AAT AAA GGC
   A  L  N  D  A  L  T  A  L  F  A  E  Q  T  N  A  T  S  T  N  K  G>

  23260                    23280                    23300                    23320
    .        .        .        .        .        .        .        .
  TTA ATC CAA TAC AAA ACA CCG GCG GGC AGT TAC TTA ACC CTA ACA CCG CTT GGC AGC AAC AAT GAC
   L  I  Q  Y  K  T  P  A  G  S  Y  L  T  L  T  P  L  G  S  N  N  D>

                23340                    23360                    23380
              .        .        .        .        .        .        .
  AAC GCC CAA GCG GGT CTT GCT TTT GTC TAT CCG GGT GTG GGA ACG GTT TAC GCC GAT ATG CTT AAT
   N  A  Q  A  G  L  A  F  V  Y  P  G  V  G  T  V  Y  A  D  M  L  N>

          23400                    23420                    23440
  .        .        .        .        .        .        .        .
  GAG CTG CAT CAG TAC TTC CCT GCG CTT TAC GCC AAA CTT GAG CGT GAA GGC GAT TTA AAG GCG ATG
   E  L  H  Q  Y  F  P  A  L  Y  A  K  L  E  R  E  G  D  L  K  A  M>

     23460                    23480                    23500
       .        .        .        .        .        .        .
  CTA CAA GCA GAA GAT ATC TAT CAT CTT GAC CCT AAA CAT GCT GCC CAA ATG AGC TTA GGT GAC TTA
   L  Q  A  E  D  I  Y  H  L  D  P  K  H  A  A  Q  M  S  L  G  D  L>

23520                    23540                    23560                    23580
  .        .        .        .        .        .        .        .
```

Fig. 4

18/30

```
GCC ATT GCT GGC GTG GGG AGC AGC TAC CTG TTA ACT CAG CTG CTC ACC GAT GAG TTT AAT ATT AAG
 A   I   A   G   V   G   S   S   Y   L   L   T   Q   L   L   T   D   E   F   N   I   K>

            23600                   23620                   23640
CCT AAT TTT GCA TTA GGT TAC TCA ATG GGT GAA GCA TCA ATG TGG GCA AGC TTA GGC GTA TGG CAA
 P   N   F   A   L   G   Y   S   M   G   E   A   S   M   W   A   S   L   G   V   W   Q>

      23660                   23680                   23700
AAC CCG CAT GCG CTG ATC AGC AAA ACC CAA ACC GAC CCG CTA TTT ACT TCT GCT ATT TCC GGC AAA
 N   P   H   A   L   I   S   K   T   Q   T   D   P   L   F   T   S   A   I   S   G   K>

23720                   23740                   23760                   23780
TTG ACC GCG GTT AGA CAA GCT TGG CAG CTT GAT GAT ACC GCA GCG GAA ATC CAG TGG AAT AGC TTT
 L   T   A   V   R   Q   A   W   Q   L   D   D   T   A   A   E   I   Q   W   N   S   F>

                23800                   23820                   23840
GTG GTT AGA AGT GAA GCA GCG CCG ATT GAA GCC TTG CTA AAA GAT TAC CCA CAC GCT TAC CTC GCG
 V   V   R   S   E   A   A   P   I   E   A   L   L   K   D   Y   P   H   A   Y   L   A>

        23860                   23880                   23900
ATT ATT CAA GGG GAT ACC TGC GTA ATC GCT GGC TGT GAA ATC CAA TGT AAA GCG CTA CTT GCA GCA
 I   I   Q   G   D   T   C   V   I   A   G   C   E   I   Q   C   K   A   L   L   A   A>

 23920                   23940                   23960                   23980
CTG GGT AAA CGC GGT ATT GCA GCT AAT CGT GTA ACG GCG ATG CAT ACG CAG CCT GCG ATG CAA GAG
 L   G   K   R   G   I   A   A   N   R   V   T   A   M   H   T   Q   P   A   M   Q   E>

                24000                   24020                   24040
CAT CAA AAT GTG ATG GAT TTT TAT CTG CAA CCG TTA AAA GCA GAG CTT CCT AGT GAA ATA AGC TTT
 H   Q   N   V   M   D   F   Y   L   Q   P   L   K   A   E   L   P   S   E   I   S   F>

            24060                   24080                   24100
ATC AGC GCC GCT GAT TTA ACT GCC AAG CAA ACG GTG AGT GAG CAA GCA CTT AGC AGC CAA GTC GTT
 I   S   A   A   D   L   T   A   K   Q   T   V   S   E   Q   A   L   S   S   Q   V   V>

      24120                   24140                   24160
GCT CAG TCT ATT GCC GAC ACC TTC TGC CAA ACC TTG GAC TTT ACC GCG CTA GTA CAT CAC GCC CAA
 A   Q   S   I   A   D   T   F   C   Q   T   L   D   F   T   A   L   V   H   H   A   Q>

24180                   24200                   24220                   24240
CAT CAA GGC GCT AAG CTG TTT GTT GAA ATT GGC GCG GAT AGA CAA AAC TGC ACC TTG ATA GAC AAG
 H   Q   G   A   K   L   F   V   E   I   G   A   D   R   Q   N   C   T   L   I   D   K>

            24260                   24280                   24300
ATT GTT AAA CAA GAT GGT GCC AGC AGT GTA CAA CAT CAA CCT TGT TGC ACA GTG CCT ATG AAC GCA
 I   V   K   Q   D   G   A   S   S   V   Q   H   Q   P   C   C   T   V   P   M   N   A>

      24320                   24340                   24360
AAA GGT AGC CAA GAT ATT ACC AGC GTG ATT AAA GCG CTT GGC CAA TTA ATT AGC CAT CAG GTG CCA
 K   G   S   Q   D   I   T   S   V   I   K   A   L   G   Q   L   I   S   H   Q   V   P>

24380                   24400                   24420                   24440
TTA TCG GTG CAA CCA TTT ATT GAT GGA CTC AAG CGC GAG CTA ACA CTT TGC CAA TTG ACC AGC CAA
 L   S   V   Q   P   F   I   D   G   L   K   R   E   L   T   L   C   Q   L   T   S   Q>

                24460                   24480                   24500
CAG CTG GCA GCA CAT GCA AAT GTT GAC AGC AAG TTT GAG TCT AAC CAA GAC CAT TTA CTT CAA GGG
 Q   L   A   A   H   A   N   V   D   S   K   F   E   S   N   Q   D   H   L   L   Q   G>

        24520                   24540                   24560
GAA GTC TA ATG TCA TTA CCA GAC AAT GCT TCT AAC CAC CTT TCT GCC AAC CAG AAA GGC GCA TCT
 E   V>
                M   S   L   P   D   N   A   S   N   H   L   S   A   N   Q   K   G   A   S>

 24580                   24600                   24620                   24640
CAG GCA AGT AAA ACC AGT AAG CAA AGC AAA ATC GCC ATT GTC GGT TTA GCC ACT CTG TAT CCA GAC
 Q   A   S   K   T   S   K   Q   S   K   I   A   I   V   G   L   A   T   L   Y   P   D>

                24660                   24680                   24700
GCT AAA ACC CCG CAA GAA TTT TGG CAG AAT TTG CTG GAT AAA CGC GAC TCT CGC AGC ACC TTA ACT
 A   K   T   P   Q   E   F   W   Q   N   L   L   D   K   R   D   S   R   S   T   L   T>
```

5 of 8

Fig. 4

19/30

```
                24720                   24740                   24760
AAC GAA AAA CTC GGC GCT AAC AGC CAA GAT TAT CAA GGT GTG CAA GGC CAA TCT GAC CGT TTT TAT
 N   E   K   L   G   A   N   S   Q   D   Y   Q   G   V   Q   G   Q   S   D   R   F   Y>

      24780                   24800                   24820
TGT AAT AAA GGC GGC TAC ATT GAG AAC TTC AGC TTT AAT GCT GCA GGC TAC AAA TTG CCG GAG CAA
 C   N   K   G   G   Y   I   E   N   F   S   F   N   A   A   G   Y   K   L   P   E   Q>

24840                   24860                   24880                   24900
AGC TTA AAT GGC TTG GAC GAC AGC TTC CTT TGG GCG CTC GAT ACT AGC CGT AAC GCA CTA ATT GAT
 S   L   N   G   L   D   D   S   F   L   W   A   L   D   T   S   R   N   A   L   I   D>

                24920                   24940                   24960
GCT GGT ATT GAT ATC AAC GGC GCT GAT TTA AGC CGC GCA GGT GTA GTC ATG GGC GCG CTG TCG TTC
 A   G   I   D   I   N   G   A   D   L   S   R   A   G   V   V   M   G   A   L   S   F>

        24980                   25000                   25020
CCA ACT ACC CGC TCA AAC GAT CTG TTT TTG CCA ATT TAT CAC AGC GCC GTT GAA AAA GCC CTG CAA
 P   T   T   R   S   N   D   L   F   L   P   I   Y   H   S   A   V   E   K   A   L   Q>

25040                   25060                   25080                   25100
GAT AAA CTA GGC GTA AAG GCA TTT AAG CTA AGC CCA ACT AAT GCT CAT ACC GCT CGC GCG GCA AAT
 D   K   L   G   V   K   A   F   K   L   S   P   T   N   A   H   T   A   R   A   A   N>

                25120                   25140                   25160
GAG AGC AGC CTA AAT GCA GCC AAT GGT GCC ATT GCC CAT AAC AGC TCA AAA GTG GTG GCC GAT GCA
 E   S   S   L   N   A   A   N   G   A   I   A   H   N   S   S   K   V   V   A   D   A>

        25180                   25200                   25220
CTT GGC CTT GGC GGC GCA CAA CTA AGC CTA GAT GCT GCC TGT GCT AGT TCG GTT TAC TCA TTA AAG
 L   G   L   G   G   A   Q   L   S   L   D   A   A   C   A   S   S   V   Y   S   L   K>

  25240                   25260                   25280                   25300
CTT GCC TGC GAT TAC CTA AGC ACT GGC AAA GCC GAT ATC ATG CTA GCA GGC GCA GTA TCT GGC GCG
 L   A   C   D   Y   L   S   T   G   K   A   D   I   M   L   A   G   A   V   S   G   A>

                25320                   25340                   25360
GAT CCT TTC TTT ATT AAT ATG GGA TTC TCA ATC TTC CAC GCC TAC CCA GAC CAT GGT ATC TCA GTA
 D   P   F   F   I   N   M   G   F   S   I   F   H   A   Y   P   D   H   G   I   S   V>

          25380                   25400                   25420
CCG TTT GAT GCC AGC AGT AAA GGT TTG TTT GCT GGC GAA GGC GCT GGC GTA TTA GTG CTT AAA CGT
 P   F   D   A   S   S   K   G   L   F   A   G   E   G   A   G   V   L   V   L   K   R>

    25440                   25460                   25480
CTT GAA GAT GCC GAG CGC GAC AAT GAC AAA ATC TAT GCG GTT GTT AGC GGC GTA GGT CTA TCA AAC
 L   E   D   A   E   R   D   N   D   K   I   Y   A   V   V   S   G   V   G   L   S   N>

25500                   25520                   25540                   25560
GAC GGT AAA GGC CAG TTT GTA TTA AGC CCT AAT CCA AAA GGT CAG GTG AAG GCC TTT GAA CGT GCT
 D   G   K   G   Q   F   V   L   S   P   N   P   K   G   Q   V   K   A   F   E   R   A>

                25580                   25600                   25620
TAT GCT GCC AGT GAC ATT GAG CCA AAA GAC ATT GAA GTG ATT GAG TGC CAC GCA ACA GGC ACA CCG
 Y   A   A   S   D   I   E   P   K   D   I   E   V   I   E   C   H   A   T   G   T   P>

        25640                   25660                   25680
CTT GGC GAT AAA ATT GAG CTC ACT TCA ATG GAA ACC TTC TTT GAA GAC AAG CTG CAA GGC ACC GAT
 L   G   D   K   I   E   L   T   S   M   E   T   F   F   E   D   K   L   Q   G   T   D>

25700                   25720                   25740                   25760
GCA CCG TTA ATT GGC TCA GCT AAG TCT AAC TTA GGC CAC CTA TTA ACT GCA GCG CAT GCG GGG ATC
 A   P   L   I   G   S   A   K   S   N   L   G   H   L   L   T   A   A   H   A   G   I>

                25780                   25800                   25820
ATG AAG ATG ATC TTC GCC ATG AAA GAA GGT TAC CTG CCG CCA AGT ATC AAT ATT AGT GAT GCT ATC
 M   K   M   I   F   A   M   K   E   G   Y   L   P   P   S   I   N   I   S   D   A   I>

          25840                   25860                   25880
GCT TCG CCG AAA AAA CTC TTC GGT AAA CCA ACC CTG CCT AGC ATG GTT CAA GGC TGG CCA GAT AAG
 A   S   P   K   K   L   F   G   K   P   T   L   P   S   M   V   Q   G   W   P   D   K>
```

Fig. 4

20/30

CAS Tum

```
25900                25920                25940                25960
CCA TCG AAT AAT CAT TTT GGT GTA AGA ACC CGT CAC GCA GGC GTA TCG GTA TTT GGC TTT GGT GGC
 P   S   N   N   H   F   G   V   R   T   R   H   A   G   V   S   V   F   G   F   G   G>

                25980                26000                26020
TGT AAC GCC CAT CTG TTG CTT GAG TCA TAC AAC GGC AAA GGA ACA GTA AAG GCA GAA GCC ACT CAA
 C   N   A   H   L   L   L   E   S   Y   N   G   K   G   T   V   K   A   E   A   T   Q>

        26040                26060                26080
GTA CCG CGT CAA GCT GAG CCG CTA AAA GTG GTT GGC CTT GCC TCG CAC TTT GGG CCT CTT AGC AGC
 V   P   R   Q   A   E   P   L   K   V   V   G   L   A   S   H   F   G   P   L   S   S>

    26100                26120                26140
ATT AAT GCA CTC AAC AAT GCT GTG ACC CAA GAT GGG AAT GGC TTT ATC GAA CTG CCG AAA AAG CGC
 I   N   A   L   N   N   A   V   T   Q   D   G   N   G   F   I   E   L   P   K   K   R>

26160                26180                26200                26220
TGG AAA GGC CTT GAA AAG CAC AGT GAA CTG TTA GCT GAA TTT GGC TTA GCA TCT GCG CCA AAA GGT
 W   K   G   L   E   K   H   S   E   L   L   A   E   F   G   L   A   S   A   P   K   G>

        26240                26260                26280
GCT TAT GTT GAT AAC TTC GAG CTG GAC TTT TTA CGC TTT AAA CTG CCG CCA AAC GAA GAT GAC CGT
 A   Y   V   D   N   F   E   L   D   F   L   R   F   K   L   P   P   N   E   D   D   R>

        26300                26320                26340
TTG ATC TCA CAG CAG CTA ATG CTA ATG CGA GTA ACA GAC GAA GCC ATT CGT GAT GCC AAG CTT GAG
 L   I   S   Q   Q   L   M   L   M   R   V   T   D   E   A   I   R   D   A   K   L   E>

26360                26380                26400                26420
CCG GGG CAA AAA GTA GCT GTA TTA GTG GCA ATG GAA ACT GAG CTT GAA CTG CAT CAG TTC CGC GGC
 P   G   Q   K   V   A   V   L   V   A   M   E   T   E   L   E   L   H   Q   F   R   G>

                26440                26460                26480
CGG GTT AAC TTG CAT ACT CAA TTA GCG CAA AGT CTT GCC GCC ATG GGC GTG AGT TTA TCA ACG GAT
 R   V   N   L   H   T   Q   L   A   Q   S   L   A   A   M   G   V   S   L   S   T   D>

        26500                26520                26540
GAA TAC CAA GCG CTT GAA GCC ATC GCC ATG GAC AGC GTG CTT GAT GCT GCC AAG CTC AAT CAG TAC
 E   Y   Q   A   L   E   A   I   A   M   D   S   V   L   D   A   A   K   L   N   Q   Y>

    26560                26580                26600                26620
ACC AGC TTT ATT GGT AAT ATT ATG GCG TCA CGC GTG GCG TCA CTA TGG GAC TTT AAT GGC CCA GCC
 T   S   F   I   G   N   I   M   A   S   R   V   A   S   L   W   D   F   N   G   P   A>

                26640                26660                26680
TTC ACT ATT TCA GCA GCA GAG CAA TCT GTG AGC CGC TGT ATC GAT GTG GCG CAA AAC CTC ATC ATG
 F   T   I   S   A   A   E   Q   S   V   S   R   C   I   D   V   A   Q   N   L   I   M>

        26700                26720                26740
GAG GAT AAC CTA GAT GCG GTG GTG ATT GCA GCG GTC GAT CTC TCT GGT AGC TTT GAG CAA GTC ATT
 E   D   N   L   D   A   V   V   I   A   A   V   D   L   S   G   S   F   E   Q   V   I>

    26760                26780                26800
CTT AAA AAT GCC ATT GCA CCT GTA GCC ATT GAG CCA AAC CTC GAA GCA AGC CTT AAT CCA ACA TCA
 L   K   N   A   I   A   P   V   A   I   E   P   N   L   E   A   S   L   N   P   T   S>

26820                26840                26860                26880
GCA AGC TGG AAT GTC GGT GAA GGT GCT GGC GCG GTC GTG CTT GTT AAA AAT GAA GCT ACA TCG GGC
 A   S   W   N   V   G   E   G   A   G   A   V   V   L   V   K   N   E   A   T   S   G>

                26900                26920                26940
TGC TCA TAC GGC CAA ATT GAT GCA CTT GGC TTT GCT AAA ACT GCC GAA ACA GCG TTG GCT ACC GAC
 C   S   Y   G   Q   I   D   A   L   G   F   A   K   T   A   E   T   A   L   A   T   D>

        26960                26980                27000
AAG CTA CTG AGC CAA ACT GCC ACA GAC TTT AAT AAG GTT AAA GTG ATT GAA ACT ATG GCA GCG CCT
 K   L   L   S   Q   T   A   T   D   F   N   K   V   K   V   I   E   T   M   A   A   P>

27020                27040                27060                27080
GCT AGC CAA ATT CAA TTA GCG CCA ATA GTT AGC TCT CAA GTG ACT CAC ACT GCT GCA GAG CAG CGT
```

Fig. 4
21/30

```
 A  S  Q  I  Q  L  A  P  I  V  S  S  Q  V  T  H  T  A  A  E  Q  R>

                27100                27120                27140
GTT GGT CAC TGC TTT GCT GCA GCG GGT ATG GCA AGC CTA TTA CAC GGC TTA CTT AAC TTA AAT ACT
 V  G  H  C  F  A  A  A  G  M  A  S  L  L  H  G  L  L  N  L  N  T>

       27160                27180                27200
GTA GCC CAA ACC AAT AAA GCC AAT TGC GCG CTT ATC AAC AAT ATC AGT GAA AAC CAA TTA TCA CAG
 V  A  Q  T  N  K  A  N  C  A  L  I  N  N  I  S  E  N  Q  L  S  Q>

 27220                27240                27260                27280
CTG TTG ATT AGC CAA ACA GCG AGC GAA CAA CAA GCA TTA ACC GCG CGT TTA AGC AAT GAG CTT AAA
 L  L  I  S  Q  T  A  S  E  Q  Q  A  L  T  A  R  L  S  N  E  L  K>

                27300                27320                27340
TCC GAT GCT AAA CAC CAA CTG GTT AAG CAA GTC ACC TTA GGT GGC CGT GAT ATC TAC CAG CAT ATT
 S  D  A  K  H  Q  L  V  K  Q  V  T  L  G  G  R  D  I  Y  Q  H  I>

          27360                27380                27400
GTT GAT ACA CCG CTT GCA AGC CTT GAA AGC ATT ACT CAG AAA TTG GCG CAA GCG ACA GCA TCG ACA
 V  D  T  P  L  A  S  L  E  S  I  T  Q  K  L  A  Q  A  T  A  S  T>

     27420                27440                27460
GTG GTC AAC CAA GTT AAA CCT ATT AAG GCC GCT GGC TCA GTC GAA ATG GCT AAC TCA TTC GAA ACG
 V  V  N  Q  V  K  P  I  K  A  A  G  S  V  E  M  A  N  S  F  E  T>

27480                27500                27520                27540
GAA AGC TCA GCA GAG CCA CAA ATA ACA ATT GCA GCA CAA CAG ACT GCA AAC ATT GGC GTC ACC GCT
 E  S  S  A  E  P  Q  I  T  I  A  A  Q  Q  T  A  N  I  G  V  T  A>

          27560                27580                27600
CAG GCA ACC AAA CGT GAA TTA GGT ACC CCA CCA ATG ACA ACA AAT ACC ATT GCT AAT ACA GCA AAT
 Q  A  T  K  R  E  L  G  T  P  P  M  T  T  N  T  I  A  N  T  A  N>

       27620                27640                27660
AAT TTA GAC AAG ACT CTT GAG ACT GTT GCT GGC AAT ACT GTT GCT AGC AAG GTT GGC TCT GGC GAC
 N  L  D  K  T  L  E  T  V  A  G  N  T  V  A  S  K  V  G  S  G  D>

27680                27700                27720                27740
ATA GTC AAT TTT CAA CAG AAC CAA CAA TTG GCT CAA CAA GCT CAC CTC GCC TTT CTT GAA AGC CGC
 I  V  N  F  Q  Q  N  Q  Q  L  A  Q  Q  A  H  L  A  F  L  E  S  R>

                27760                27780                27800
AGT GCG GGT ATG AAG GTG GCT GAT GCT TTA TTG AAG CAA CAG CTA GCT CAA GTA ACA GGC CAA ACT
 S  A  G  M  K  V  A  D  A  L  L  K  Q  Q  L  A  Q  V  T  G  Q  T>

       27820                27840                27860
ATC GAT AAT CAG GCC CTC GAT ACT CAA GCC GTC GAT ACT CAA ACA AGC GAG AAT GTA GCG ATT GCC
 I  D  N  Q  A  L  D  T  Q  A  V  D  T  Q  T  S  E  N  V  A  I  A>

 27880                27900                27920                27940
GCA GAA TCA CCA GTT CAA GTT ACA ACA CCT GTT CAA GTT ACA ACA CCT GTT CAA ATC AGT GTT GTG
 A  E  S  P  V  Q  V  T  T  P  V  Q  V  T  T  P  V  Q  I  S  V  V>

                27960                27980                28000
GAG TTA AAA CCA GAT CAC GCT AAT GTG CCA CCA TAC ACG CCG CCA GTG CCT GCA TTA AAG CCG TGT
 E  L  K  P  D  H  A  N  V  P  P  Y  T  P  P  V  P  A  L  K  P  C>

          28020                28040                28060
ATC TGG AAC TAT GCC GAT TTA GTT GAG TAC GCA GAA GGC GAT ATC GCC AAG GTA TTT GGC AGT GAT
 I  W  N  Y  A  D  L  V  E  Y  A  E  G  D  I  A  K  V  F  G  S  D>

     28080                28100                28120
TAT GCC ATT ATC GAC AGC TAC TCG CGC CGC GTA CGT CTA CCG ACC ACT GAC TAC CTG TTG GTA TCG
 Y  A  I  I  D  S  Y  S  R  R  V  R  L  P  T  T  D  Y  L  L  V  S>

28140                28160                28180                28200
CGC GTG ACC AAA CTT GAT GCG ACC ATC AAT CAA TTT AAG CCA TGC TCA ATG ACC ACT GAG TAC GAC
 R  V  T  K  L  D  A  T  I  N  Q  F  K  P  C  S  M  T  T  E  Y  D>

                28220                28240                28260
```

Fig. 4
22/30

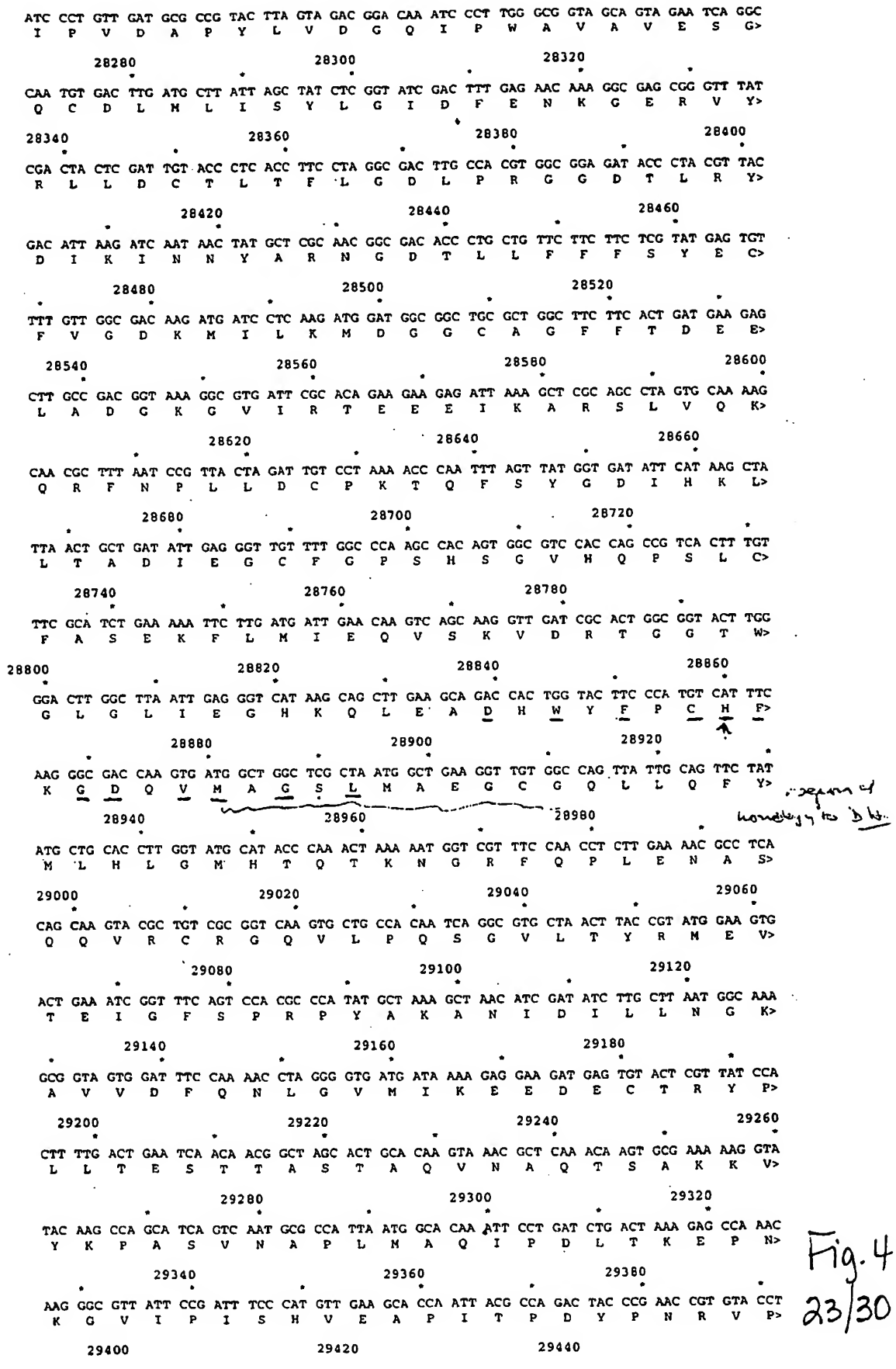
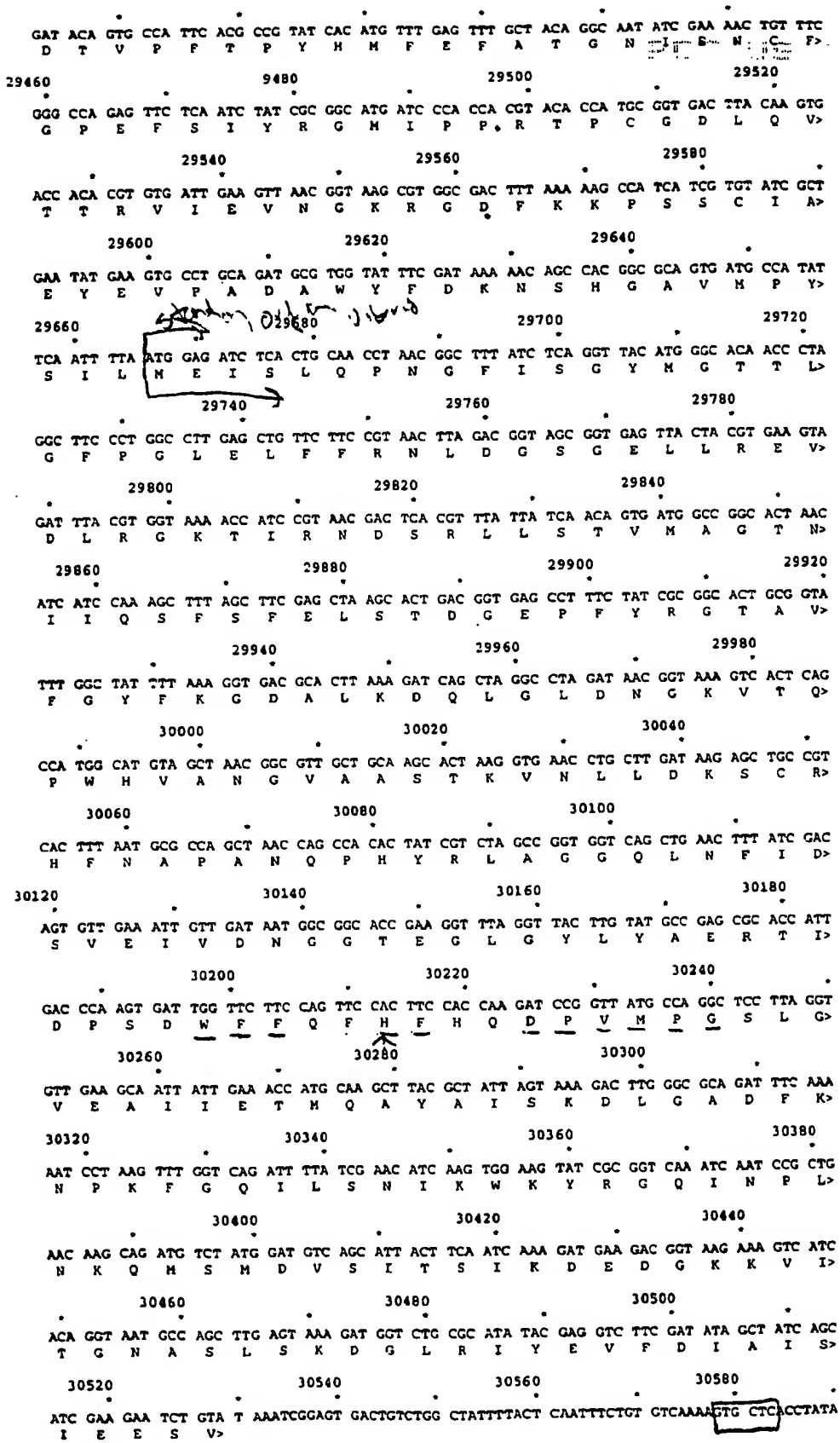

ATC CCT GTT GAT GCG CCG TAC TTA GTA GAC GGA CAA ATC CCT TGG GCG GTA GCA GTA GAA TCA GGC
I P V D A P Y L V D G Q I P W A V A V E S G>
28280
28300
28320
CAA TGT GAC TTG ATG CTT ATT AGC TAT CTC GGT ATC GAC TTT GAG AAC AAA GGC GAG CGG GTT TAT
Q C D L M L I S Y L G I D F E N K G E R V Y>
28340
28360
28380
28400
CGA CTA CTC GAT TGT ACC CTC ACC TTC CTA GGC GAC TTG CCA CGT GGC GGA GAT ACC CTA CGT TAC
R L L D C T L T F L G D L P R G G D T L R Y>
28420
28440
28460
GAC ATT AAG ATC AAT AAC TAT GCT CGC AAC GGC GAC ACC CTG CTG TTC TTC TTC TCG TAT GAG TGT
D I K I N N Y A R N G D T L L F F F S Y E C>
28480
28500
28520
TTT GTT GGC GAC AAG ATG ATC CTC AAG ATG GAT GGC GGC TGC GCT GGC TTC TTC ACT GAT GAA GAG
F V G D K M I L K M D G G C A G F F T D E E>
28540
28560
28580
28600
CTT GCC GAC GGT AAA GGC GTG ATT CGC ACA GAA GAA GAG ATT AAA GCT CGC AGC CTA GTG CAA AAG
L A D G K G V I R T E E E I K A R S L V Q K>
28620
28640
28660
CAA CGC TTT AAT CCG TTA CTA GAT TGT CCT AAA ACC CAA TTT AGT TAT GGT GAT ATT CAT AAG CTA
Q R F N P L L D C P K T Q F S Y G D I H K L>
28680
28700
28720
TTA ACT GCT GAT ATT GAG GGT TGT TTT GGC CCA AGC CAC AGT GGC GTC CAC CAG CCG TCA CTT TGT
L T A D I E G C F G P S H S G V H Q P S L C>
28740
28760
28780
TTC GCA TCT GAA AAA TTC TTG ATG ATT GAA CAA GTC AGC AAG GTT GAT CGC ACT GGC GGT ACT TGG
F A S E K F L M I E Q V S K V D R T G G T W>
28800
28820
28840
28860
GGA CTT GGC TTA ATT GAG GGT CAT AAG CAG CTT GAA GCA GAC CAC TGG TAC TTC CCA TGT CAT TTC
G L G L I E G H K Q L E A D H W Y F P C H F>
28880
28900
28920
AAG GGC GAC CAA GTG ATG GCT GGC TCG CTA ATG GCT GAA GGT TGT GGC CAG TTA TTG CAG TTC TAT
K G D Q V M A G S L M A E G C G Q L L Q F Y>
28940
28960
28980
ATG CTG CAC CTT GGT ATG CAT ACC CAA ACT AAA AAT GGT CGT TTC CAA CCT CTT GAA AAC GCC TCA
M L H L G M H T Q T K N G R F Q P L E N A S>
29000
29020
29040
29060
CAG CAA GTA CGC TGT CGC GGT CAA GTG CTG CCA CAA TCA GGC GTG CTA ACT TAC CGT ATG GAA GTG
Q Q V R C R G Q V L P Q S G V L T Y R M E V>
29080
29100
29120
ACT GAA ATC GGT TTC AGT CCA CGC CCA TAT GCT AAA GCT AAC ATC GAT ATC TTG CTT AAT GGC AAA
T E I G F S P R P Y A K A N I D I L L N G K>
29140
29160
29180
GCG GTA GTG GAT TTC CAA AAC CTA GGG GTG ATG ATA AAA GAG GAA GAT GAG TGT ACT CGT TAT CCA
A V V D F Q N L G V M I K E E D E C T R Y P>
29200
29220
29240
29260
CTT TTG ACT GAA TCA ACA ACG GCT AGC ACT GCA CAA GTA AAC GCT CAA ACA AGT GCG AAA AAG GTA
L L T E S T T A S T A Q V N A Q T S A K K V>
29280
29300
29320
TAC AAG CCA GCA TCA GTC AAT GCG CCA TTA ATG GCA CAA ATT CCT GAT CTG ACT AAA GAG CCA AAC
Y K P A S V N A P L M A Q I P D L T K E P N>
29340
29360
29380
AAG GGC GTT ATT CCG ATT TCC CAT GTT GAA GCA CCA ATT ACG CCA GAC TAC CCG AAC CGT GTA CCT
K G V I P I S H V E A P I T P D Y P N R V P>
29400
29420
29440

Fig. 4

23/30



— exact match w/ FAGA

Fig. 4

24/30

```
      30600                 30620                 30640                 30660
TTCATAGGCT GCGCGCTTTT TTCTGGAAAT TGAGCAAAAG TATCTGCGTC CTAACTCGAT TTATAAGAAT GGTTTAATTG

      30680                 30700                 30720                 30740
AAAAGAACAA CAGCTAAGAG CCGCAAGCTC AATATAAATA ATTAAGGGTC TTACAAATA ATG AAT CCT ACA GCA ACT
                                                                    M   N   P   T   A   T>

            30760                 30780                 30800
AAC GAA ATG CTT TCT CCG TGG CCA TGG GCT GTG ACA GAG TCA AAT ATC AGT TTT GAC GTG CAA GTG
 N   E   M   L   S   P   W   P   W   A   V   T   E   S   N   I   S   F   D   V   Q   V>

      30820                 30840                 30860
ATG GAA CAA CAA CTT AAA GAT TTT AGC CGG GCA TGT TAC GTG GTC AAT CAT GCC GAC CAC GGC TTT
 M   E   Q   Q   L   K   D   F   S   R   A   C   Y   V   V   N   H   A   D   H   G   F>

30880                 30900                 30920                 30940
GGT ATT GCG CAA ACT GCC GAT ATC GTG ACT GAA CAA GCG GCA AAC AGC ACA GAT TTA CCT GTT AGT
 G   I   A   Q   T   A   D   I   V   T   E   Q   A   A   N   S   T   D   L   P   V   S>

            30960                 30980                 31000
GCT TTT ACT CCT GCA TTA GGT ACC GAA AGC CTA GGC GAC AAT AAT TTC CGC CGC GTT CAC GGC GTT
 A   F   T   P   A   L   G   T   E   S   L   G   D   N   N   F   R   R   V   H   G   V>

      31020                 31040                 31060
AAA TAC GCT TAT TAC GCA GGC GCT ATG GCA AAC GGT ATT TCA TCT GAA GAG CTA GTG ATT GCC CTA
 K   Y   A   Y   Y   A   G   A   M   A   N   G   I   S   S   E   E   L   V   I   A   L>

31080                 31100                 31120                 31140
GGT CAA GCT GGC ATT TTG TGT GGT TCG TTT GGA GCA GCC GGT CTT ATT CCA AGT CGC GTT GAA GCG
 G   Q   A   G   I   L   C   G   S   F   G   A   A   G   L   I   P   S   R   V   E   A>

            31160                 31180                 31200
GCA ATT AAC CGT ATT CAA GCA GCG CTG CCA AAT GGC CCT TAT ATG TTT AAC CTT ATC CAT AGT CCT
 A   I   N   R   I   Q   A   A   L   P   N   G   P   Y   M   F   N   L   I   H   S   P>

      31220                 31240                 31260
AGC GAG CCA GCA TTA GAG CGT GGC AGC GTA GAG CTA TTT TTA AAG CAT AAG GTA CGC ACC GTT GAA
 S   E   P   A   L   E   R   G   S   V   E   L   F   L   K   H   K   V   R   T   V   E>

31280                 31300                 31320                 31340
GCA TCA GCT TTC TTA GGT CTA ACA CCA CAA ATC GTC TAT TAC CGT GCA GCA GGA TTG AGC CGA GAC
 A   S   A   F   L   G   L   T   P   Q   I   V   Y   Y   R   A   A   G   L   S   R   D>

                  31360                 31380                 31400
GCA CAA GGT AAA GTT GTG GTT GGT AAC AAG GTT ATC GCT AAA GTA AGT CGC ACC GAA GTG GCT GAA
 A   Q   G   K   V   V   V   G   N   K   V   I   A   K   V   S   R   T   E   V   A   E>

            31420                 31440                 31460
AAG TTT ATG ATG CCA GCG CCC GCA AAA ATG CTA CAA AAA CTA GTT GAT GAC GGT TCA ATT ACC GCT
 K   F   M   M   P   A   P   A   K   M   L   Q   K   L   V   D   D   G   S   I   T   A>

      31480                 31500                 31520
GAG CAA ATG GAG CTG GCG CAA CTT GTA CCT ATG GCT GAC GAC ATC ACT GCA GAG GCC GAT TCA GGT
 E   Q   M   E   L   A   Q   L   V   P   M   A   D   D   I   T   A   E   A   D   S   G>

31540                 31560                 31580                 31600
GGC CAT ACT GAT AAC CGT CCA TTA GTA ACA TTG CTG CCA ACC ATT TTA GCG CTG AAA GAA GAA ATT
 G   H   T   D   N   R   P   L   V   T   L   L   P   T   I   L   A   L   K   E   E   I>

            31620                 31640                 31660
CAA GCT AAA TAC CAA TAC GAC ACT CCT ATT CGT GTC GGT TGT GGT GGC GGT GTG GGT ACG CCT GAT
 Q   A   K   Y   Q   Y   D   T   P   I   R   V   G   C   G   G   G   V   G   T   P   D>

      31680                 31700                 31720
GCA GCG CTG GCA ACG TTT AAC ATG GGC GCG GCG TAT ATT GTT ACC GGC TCT ATC AAC CAA GCT TGT
 A   A   L   A   T   F   N   M   G   A   A   Y   I   V   T   G   S   I   N   Q   A   C>

31740                 31760                 31780                 31800
GTT GAA GCG GGC GCA AGT GAT CAC ACT CGT AAA TTA CTT GCC ACC ACT GAA ATG GCC GAT GTG ACT
 V   E   A   G   A   S   D   H   T   R   K   L   L   A   T   T   E   M   A   D   V   T>
```

0-89

Fig. 4

25/30

```
                31820                 31840                 31860
ATG GCA CCA GCT GCA GAT ATG TTC GAG ATG GGC GTA AAA CTG CAG GTG GTT AAG CGC GGC ACG CTA
 M   A   P   A   A   D   M   F   E   M   G   V   K   L   Q   V   V   K   R   G   T   L>

        31880                 31900                 31920
TTC CCA ATG CGC GCT AAC AAG CTA TAT GAG ATC TAC ACG CGT TAC GAT TCA ATC GAA GCG ATC CCA
 F   P   M   R   A   N   K   L   Y   E   I   Y   T   R   Y   D   S   I   E   A   I   P>

31940                 31960                 31980                 32000
TTA GAC GAG CGT GAA AAG CTT GAG AAA CAA GTA TTC CGC TCA AGC CTA GAT GAA ATA TGG GCA GGT
 L   D   E   R   E   K   L   E   K   Q   V   F   R   S   S   L   D   E   I   W   A   G>

                32020                 32040                 32060
ACA GTG GCG CAC TTT AAC GAG CGC GAC CCT AAG CAA ATC GAA CGC GCA GAG GGT AAC CCT AAG CGT
 T   V   A   H   F   N   E   R   D   P   K   Q   I   E   R   A   E   G   N   P   K   R>

            32080                 32100                 32120
AAA ATG GCA TTG ATT TTC CGT TGG TAC TTA GGT CTT TCT AGT CGC TGG TCA AAC TCA GGC GAA GTG
 K   M   A   L   I   F   R   W   Y   L   G   L   S   S   R   W   S   N   S   G   E   V>

    32140                 32160                 32180
GGT CGT GAA ATG GAT TAT CAA ATT TGG GCT GGC CCT GCT CTC GGT GCA TTT AAC CAA TGG GCA AAA
 G   R   E   M   D   Y   Q   I   W   A   G   P   A   L   G   A   F   N   Q   W   A   K>

32200                 32220                 32240                 32260
GGC AGT TAC TTA GAT AAC TAT CAA GAC CGA AAT GCC GTC GAT TTG GCA AAG CAC TTA ATG TAC GGC
 G   S   Y   L   D   N   Y   Q   D   R   N   A   V   D   L   A   K   H   L   M   Y   G>

            32280                 32300                 32320
GCG GCT TAC TTA AAT CGT ATT AAC TCG CTA ACG GCT CAA GGC GTT AAA GTG CCA GCA CAG TTA CTT
 A   A   Y   L   N   R   I   N   S   L   T   A   Q   G   V   K   V   P   A   Q   L   L>

        32340                 32360                 32380                 32400
CGC TGG AAG CCA AAC CAA AGA ATG GCC TA ATACACTTAC AAAGCACCAG TCTAAAAAGC CACTAATCTT
 R   W   K   P   N   Q   R   M   A>

                32420                 32440                 32460                 32480
GATTAGTGGC TTTTTTTATT GTGGTCAATA TGAGGCTATT TAGCCTGTAA GCCTGAAAAT ATCAGCACTC TGACTTTACA

                32500                 32520                 32540                 32560
AGCAAATTAT AATTAAGGCA GGGCTCTACT CATTTATACT GCTAGCAAAC AAGCAAGTTG CCCAGTAAAA CAACAAGGTA

                32580                 32600                 32620                 32640
CCTGATTTAT ATCGTCATAA AAGTTGGCTA GAGATTCGTT ATTGATCTTT ACTGATTAGA GTCGCTCTGT TTGGAAAAAG

                32660                 32680                 32700                 32720
GTTTCTCGTT ATCATCAAAA TACACTCTCA AACCTTTAAT CAATTACAAC TTAGGCTTTC TGCGGGCATT TTTATCTTAT

                32740                 32760                 32780                 32800
TTGCCACAGC TGTATTTGCC TTTAGGTTTT GGGTGCAACT ACCATTAATT GAGGCCTCAT TAGTTAAATT ATCTGAGCAA

                32820                 32840                 32860
GAGCTCACCT CTTTAAATTA CGCTTTTCAG CAA ATG AGA AAG CCA CTA CAA ACC ATT AAT TAC GAC TAT GCG
                                       M   R   K   P   L   Q   T   I   N   Y   D   Y   A>

        32880                 32900                 32920
GTG TGG GAC AGA ACC TAC AGC TAT ATG AAA TCA AAC TCA GCG AGC GCT AAA AGG TAC TAT GAA AAA
 V   W   D   R   T   Y   S   Y   M   K   S   N   S   A   S   A   K   R   Y   Y   E   K>

32940                 32960                 32980                 33000
CAT GAG TAC CCA GAT GAT ACG TTC AAG AGT TTA AAA GTC GAC GGA GTA TTT ATA TTC AAC CGT ACA
 H   E   Y   P   D   D   T   F   K   S   L   K   V   D   G   V   F   I   F   N   R   T>

                33020                 33040                 33060
AAT CAG CCA GTT TTT AGT AAA GGT TTT AAT CAT AGA AAT GAT ATA CCG CTG GTC TTT GAA TTA ACT
 N   Q   P   V   F   S   K   G   F   N   H   R   N   D   I   P   L   V   F   E   L   T>

        33080                 33100                 33120
GAC TTT AAA CAA CAT CCA CAA AAC ATC GCA TTA TCT CCA CAA ACC AAA CAG GCA CAC CCA CCG GCA
 D   F   K   Q   H   P   Q   N   I   A   L   S   P   Q   T   K   Q   A   H   P   P   A>
```

Fig. 4
26/30

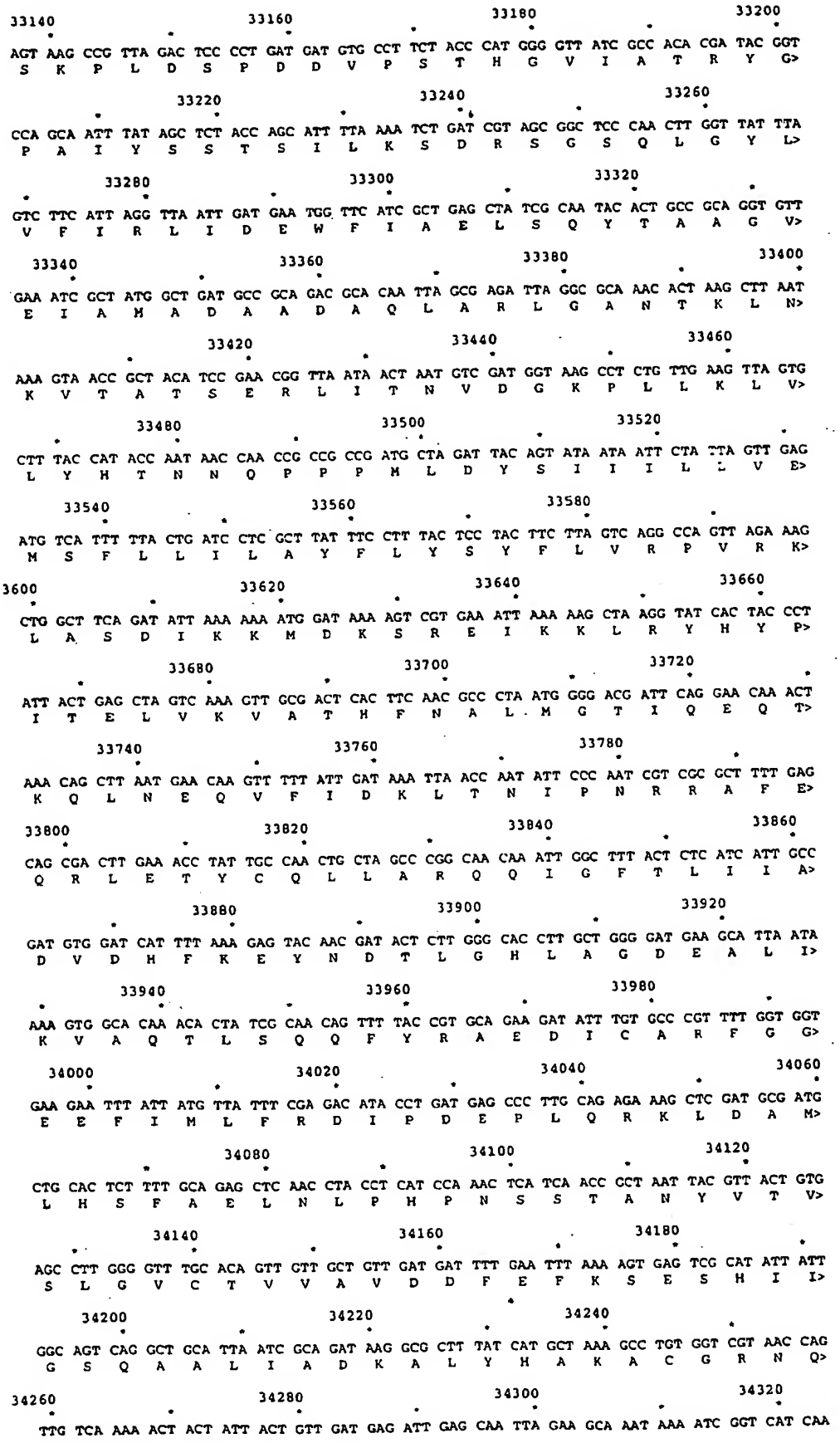

33140 33160 33180 33200
AGT AAG CCG TTA GAC TCC CCT GAT GAT GTG CCT TCT ACC CAT GGG GTT ATC GCC ACA CGA TAC GGT
S K P L D S P D D V P S T H G V I A T R Y G>
33220 33240 33260
CCA GCA ATT TAT AGC TCT ACC AGC ATT TTA AAA TCT GAT CGT AGC GGC TCC CAA CTT GGT TAT TTA
P A I Y S S T S I L K S D R S G S Q L G Y L>
33280 33300 33320
GTC TTC ATT AGG TTA ATT GAT GAA TGG TTC ATC GCT GAG CTA TCG CAA TAC ACT GCC GCA GGT GTT
V F I R L I D E W F I A E L S Q Y T A A G V>
33340 33360 33380 33400
GAA ATC GCT ATG GCT GAT GCC GCA GAC GCA CAA TTA GCG AGA TTA GGC GCA AAC ACT AAG CTT AAT
E I A M A D A A D A Q L A R L G A N T K L N>
33420 33440 33460
AAA GTA ACC GCT ACA TCC GAA CGG TTA ATA ACT AAT GTC GAT GGT AAG CCT CTG TTG AAG TTA GTG
K V T A T S E R L I T N V D G K P L L K L V>
33480 33500 33520
CTT TAC CAT ACC AAT AAC CAA CCG CCG CCG ATG CTA GAT TAC AGT ATA ATA ATT CTA TTA GTT GAG
L Y H T N N Q P P P M L D Y S I I I L L V E>
33540 33560 33580
ATG TCA TTT TTA CTG ATC CTC GCT TAT TTC CTT TAC TCC TAC TTC TTA GTC AGG CCA GTT AGA AAG
M S F L L I L A Y F L Y S Y F L V R P V R K>
33600 33620 33640 33660
CTG GCT TCA GAT ATT AAA AAA ATG GAT AAA AGT CGT GAA ATT AAA AAG CTA AGG TAT CAC TAC CCT
L A S D I K K M D K S R E I K K L R Y H Y P>
33680 33700 33720
ATT ACT GAG CTA GTC AAA GTT GCG ACT CAC TTC AAC GCC CTA ATG GGG ACG ATT CAG GAA CAA ACT
I T E L V K V A T H F N A L M G T I Q E Q T>
33740 33760 33780
AAA CAG CTT AAT GAA CAA GTT TTT ATT GAT AAA TTA ACC AAT ATT CCC AAT CGT CGC GCT TTT GAG
K Q L N E Q V F I D K L T N I P N R R A F E>
33800 33820 33840 33860
CAG CGA CTT GAA ACC TAT TGC CAA CTG CTA GCC CGG CAA CAA ATT GGC TTT ACT CTC ATC ATT GCC
Q R L E T Y C Q L L A R Q Q I G F T L I I A>
33880 33900 33920
GAT GTG GAT CAT TTT AAA GAG TAC AAC GAT ACT CTT GGG CAC CTT GCT GGG GAT GAA GCA TTA ATA
D V D H F K E Y N D T L G H L A G D E A L I>
33940 33960 33980
AAA GTG GCA CAA ACA CTA TCG CAA CAG TTT TAC CGT GCA GAA GAT ATT TGT GCC CGT TTT GGT GGT
K V A Q T L S Q Q F Y R A E D I C A R F G G>
34000 34020 34040 34060
GAA GAA TTT ATT ATG TTA TTT CGA GAC ATA CCT GAT GAG CCC TTG CAG AGA AAG CTC GAT GCG ATG
E E F I M L F R D I P D E P L Q R K L D A M>
34080 34100 34120
CTG CAC TCT TTT GCA GAG CTC AAC CTA CCT CAT CCA AAC TCA TCA ACC GCT AAT TAC GTT ACT GTG
L H S F A E L N L P H P N S S T A N Y V T V>
34140 34160 34180
AGC CTT GGG GTT TGC ACA GTT GTT GCT GTT GAT GAT TTT GAA TTT AAA AGT GAG TCG CAT ATT ATT
S L G V C T V V A V D D F E F K S E S H I I>
34200 34220 34240
GGC AGT CAG GCT GCA TTA ATC GCA GAT AAG GCG CTT TAT CAT GCT AAA GCC TGT GGT CGT AAC CAG
G S Q A A L I A D K A L Y H A K A C G R N Q>
34260 34280 34300 34320
TTG TCA AAA ACT ACT ATT ACT GTT GAT GAG ATT GAG CAA TTA GAA GCA AAT AAA ATC GGT CAT CAA

Fig. 4

27/30

```
L  S  K  T  T  I  T  V  D  E  I  E  Q  L  E  A  N  K  I  G  H  Q>

          34340               34360               34380               34400
GCC TAA ACTCGTTCGA GTACTTTCCC CTAAGTCAGA GCTATTTGCC ACTTCAAGAT GTGGCTACAA GGCTTACTCT
A>

          34420               34440               34460               34480
TTCAAAACCT GCATCAATAG AACACAGCAA AATACAATAA TTTAAGTCAA TTTAGCCTAT TAAACAGAGT TAATGACAGC

          34500               34520               34540               34560
TCATGGTCGC AACTTATTAG CTATTTCTAG CAATATAAAA ACTTATCCAT TAGTAGTAAC CAATAAAAAA ACTAATATAT

          34580               34600               34620               34640
AAAACTATTT AATCATTATT TTACAGATGA TTAGCTACCA CCCACCTTAA GCTGGCTATA TTCGCACTAG TAAAAATAAA

          34660               34680               34700               34720
CATTAGATCG GGTTCAGATC AATTTACGAG TCTCGTATAA AATGTACAAT AATTCACTTA ATTTAATACT GCATATTTTT

          34740               34760               34780               34800
ACAAGTAGAG AGCGGTGATG AAACAAAATA CGAAAGGCTT TACATTAATT GAATTAGTCA TCGTGATTAT TATTCTCGGT

          34820               34840               34860               34880
ATACTTGCTG CTGTGGCACT GCCGAAATTC ATCAATGTTC AAGATGACGC TAGGATCTCT GCGATGAGCG GTCAGTTTTC

          34900               34920               34940               34960
ATCATTTGAA AGTGCCGTAA AACTATACCA TAGCGGTTGG TTAGCCAAAG GCTACAACAC TGCGGTTGAA AAGCTCTCAG

          34980               35000               35020               35040
GCTTTGGCCA AGGTAATGTT GCATCAAGTG ACACAGGTTT TCCGTACTCA ACATCAGGCA CGAGTACTGA TGTGCATAAA

          35060               35080               35100               35120
GCTTGTGGTG AACTATGGCA TGGCATTACC GATACAGACT TCACAATTGG TGCGGTTAGT GATGGCGATC TAATGACTGC

          35140               35160               35180               35200
AGATGTCGAT ATTGCTTACA CCTATCGTGG TGATATGTGT ATCTATCGCG ATCTGTATTT TATTCAGCGC TCATTACCTA

          35220               35240               35260               35280
CTAAGGTGAT GAACTACAAA TTTAAAACTG GTGAAATAGA AATTATTGAT GCTTTCTACA ACCCTGACGG CTCAACTGGT

          35300               35320               35340               35360
CAATTACCAT AAATTTGGCG CTTATCTAAG TTGTACTTGC TCTGACCGAC ACAAATAATG TCGTTTCTCA GCATATATCA

          35380               35400               35420               35440
AAATACACAG CAAAAATTTG GGGTTAGCTA TATAGCTAAC CCCAAATCAT ATCTAACTTT ACACTGCATC TAATTCCAAA

          35460               35480               35500               35520
CAGTATCCAG CCAAAAGCCT AAACTATTGT TGACTCAGCG CTAAAATATG CGATGCAACA AACAAGTCTT GGATCGCAAT

          35540               35560               35580               35600
ACCTGAGCTA TCAAAAATGG TCACCTCATC AGCACTTTGA CGTCCTGTTG CGGACTCGTT TATCACCTGA CCAATCTCAA

          35620               35640               35660               35680
TTATCGGCGT ATTTCTGCTA TGTTGAAACT CACCAATAAC AATAGATTGA GAAGCAAAGT CGCAAAACAA GCGAGCATGA

          35700               35720               35740               35760
CTATATAGGT CAGTTGGCAA CTCTTGCTTA CCCACTTTAT CAGCGCCCAT TGCAGAAATA TGCGTTCCTG CTTGTACCCA

          35780               35800               35820               35840
CTGCGCTTCA AATAAAGGCG CTTGAGCTGT GGTTGCTGTG ATAATAATAT CTGCTTGTTC ACAAGCAGCT TGTGCATCAC

          35860               35880               35900               35920
AAGCTTCGGC ATTAATGCCT TTTTCTAATA AACGCTTAAC CAAGTTTTCA GTTTTGCTAG CACTACGGCC AACTACCAAT

          35940               35960               35980               36000
ACCTTAGTTA ATGAACGAAC CTTGCTCACT GCTAGCACTT CATATTCAGC CTGATGACCG GTACCAAAAA CAGTTAATAC

          36020               36040               36060               36080
```

Fig. 4
28/30

```
CGTAGCATCT TCTCTCGCGA GGTAACTCAC TGCTACTGCA TCGGCAGCAC CAGTGCGGTA AGCATTAACG GTAGTGGCAG

                36100               36120               36140               36160
CAATCACCGN CTGCAACATA CCGGTTAATG GATCGAGTAA AAATACGTTA GTGCCGTGGC ATGGTAAACC ATGTTTATGG

                36180               36200               36220               36240
TTATCAGGCC AATAGCTGCC TGTTTTCCAG CCGACAAGGT TTGGCGTTGA AGCCGACTTT AATGAGAACA TTTCATTAAG

                36260               36280               36300               36320
GTTCGCGCCC TGTGCATTAA CTACCGGGAA CAAGGTTGCT TTATCATCTA CGGCAGCGAC AAACGCTTCT TTAACAGCGA

                36340               36360               36380               36400
TATAAGCCAG CTCATGGGAG ATGAGCTTTG ATGTTTGCGC TTCAGTTAAA TAGATCATAT TACCACCCCT GCACTCGATT

                36420               36440               36460               36480
CCAGATCTCA TAGCCACCAT TATCACCATC AGTATCAAAT ACATGGTACT GAGCGTGCAT TGAAGCTGTT GCACAGGCGT

                36500               36520               36540               36560
GGTTCGGCAA AATATGTAGA CGACTACCTA CCGGGAACTG CGCTAAATCA ATAACGCCGC CATCAACTGC TTCAATAATG

                36580               36600               36620               36640
CCGTGCTCTT GATTAACAGT TATAACCTGT AGACCTGATA ACACGTGACC GCTGTCGTCA CACACTAAAC CATAACCACA

                36660               36680               36700               36720
ATCTTTTGGC TGCTCTGCAG TACCTCTATC ACCCGAAAGA GCCATCCAAC CCGCATCAAT GAAAATCCAG TTTTTATCAG

                36740               36760               36780               36800
GATTATGACC AATAACACTG GTCACTACCG TTGCGGCAAT ATCAGTTAAC TGACACACGT TTAGCCCTGC CATGACTAAA

                36820               36840               36860               36880
TCGAAGAAGG TGTACACACC CGCTCTAACC TCGGTGATCC CATCAAGGTT TTGATAGCTT TGCGCTGTTG GTGTTGAACC

                36900               36920               36940               36960
AATACTAACG ATGTCACATT GCATACCCGC TGCGCGAATG CGTCAGCAGC TTGTACAGCC GCTGCAACTT CATTTTGCGC

                36980               37000               37020               37040
CGCATCAATT AATTGCTGTT TTTCAAAACA TTGATATGAC TCACCAGCGT GAGTNAGTAC GCCGTGAAAA CTCGCTGCGC

                37060               37080               37100               37120
CAGACGTTAG TATCTGAGCA ATTTCAATCA ACTTATCGGC TTCCGGTGGA ATACCACCAC GATGGCCATC ACAATCAATT

                37140               37160               37180               37200
TCAATTAATG CTGGTATTTG GCAGTCATAA GAACCACAGA AATGATTTAG CTGATGCGCT TGCTCAACAC TATCAAGTAA

                37220               37240               37260               37280
AACTCTTGCA TTAATACCTT GGTCCAACAT TTTAGCAATA CGCGGCAACT TACCATCGGC AATACCTACT GCATAAATAA

                37300               37320               37340               37360
TGTCTGTGTA ACCTTTAGAT GCTAAGGCCT CGGCCTCTTT TACCGTTGAT ACAGTGACTG GTGAGTTTTT AGTGGGTAAT

                37380               37400               37420               37440
AAAAACTCGG CTGCTTCAAG TGATCTTAAC GTTTTAAAAT GCGGTCTTAG GTTTGCACCT AATCCTTCAA TTTTTTGGCG

                37460               37480               37500               37520
TAGTTGACTG AGGTTATTAA TAAATACTGG CTTATTTACA TATAAAAACG GTGTATCAAT TGCTTGATAC TGACTTTGCT

                37540               37560               37580               37600
GAGTCGTGGA AAGTATTTGA GTAGATGGCA TCTTTAATAT CCTAGTTCAT CAATCAATCT AACAAGTTTG ATGCCTAGCC

                37620               37640               37660               37680
ACAGTGGCTT GTATTCATGA TGCTTTGGAA AATGCTTATA TTCAAAGTAT TTGAAAGACA TCAAACTTCT TGTTTAATGC

                37700               37720               37740               37760
TCAGTATCCA CCAGCACGCA TTTATTTTAT ATTAACTATT ATCAAGATAT AGATTAGGTT CAAACCAAAT GATTAGTACT

                37780               37800               37820               37840
GAAGATCTAC GTTTTATCAG CGTAATCGCC AGTCATCGCA CCTTAGCTGA TGCCGCTAGA ACACTAAATA TCACGCCACC
```

Fig. 4

29/30

```
          37860                37880
ATCAGTGACA TTAAGGTTGC AGCATATTGA AAAGAAACTA TCGATTAGCC TGATC
```

Fig. 4
30/30

```
        10         20         30         40         50         60
AATAGATCGACTCGCAAAAGTTGCTTAAGATAGTGTCAATATAGCTTCTTATTTGTAAAT

        70         80         90        100        110        120
ATTGTTTTTTATGTGTAAACATGTTTAGTGTGTGTAAATGCTGTTAATTATCCTTTTGGG

       130        140        150        160        170        180
ATTGTAATAGCTGATGTTGCTGGCTAATGAGTACTTTTAGTTCGGCAATATCTTGCTTTA

       190        200        210        220        230        240
AATCGCTAACTTCAGTTTTTAATTCACCCACACTTGTTGTATTTTTAAGGCTCTCTTCCC

       250        260        270        280        290        300
CACCATCGACAAACCAGGATGATATGAAACCGGTAAACGTACCAAAGAGACCGACACCTG

       310        320        330        340        350        360
CAGTCATGAGTAATGCCGCAATGATACGTCCGCCAGTGGTGACGGGGTAGTAGTCACCGT

       370        380        390        400        410        420
AACCAACAGTCGTTATTGTCACAAATGACCACCAAAGTGCGTCGATGCCGTTATTGATGT

       430        440        450        460        470        480
TACTGCCTACTTGATCCTGTTCTAACAATAAAATACCGATAGCACCAAAGGTGACAAGGA

       490        500        510        520        530        540
TGAAGGATATCGCAGATACCAGCGAAAAGGTGGCTTTAAACCGATGTTCAAAAATCATTT

       550        560        570        580        590        600
TTAAGATAATTTTTGATGAGCGTATATTCTGAATAGATCTTAATACTCTAGCGATACGAA

       610        620        630        640        650        660
TTATGCGAATAAACTGCAGTTGCTCGACCATCGGAATACTCGACAGTAGGTCAATCCAAC

       670        680        690        700        710        720
CCCATTTCATAAACTGAAATTTATTCTCAGCTTGGTGAAAGCGAATTACAAAGTCAGTGA

       730        740        750        760        770        780
AAAAGAATAAGCAAATCGTATTATCTACGCTCGTTAATATTTCAGTGACGTTACTTGAAA

       790        800        810        820        830        840
AGGTAAAAATAAGTTGCAGTAGTGATGATACGACCACATGAAGTGATAAAATAAGCATGA

       850        860        870        880        890        900
AAATCTGAAATGGATTTACATCACTGTTGTTTTTGGTGCCACTTTTAAGGTTCGTTTTCA

       910        920        930        940        950        960
CAATCTGCTGCCTCGGTTCATTGATTTTGTTAATATAAACCTTAGTCAGTAGCAAGACAA

       970        980        990       1000       1010       1020
AATATATTTACATCAATGTCATCGTATTATTCAACCGCGCGTCGTGTATTCAGACCAAGA

      1030       1040       1050       1060       1070       1080
TCGTTGTATATGTTAGTCATGTAGCGATGAGATTATCATGCGACAGGAGAGAATTATGTT

      1090       1100       1110       1120       1130       1140
TGTTATTATTTTTTACGTACCTAAAGTTAATGTTGAAGAAGTAAAACAGGCGTTATTTAA
```

Fig. 5

```
      1150       1160       1170       1180       1190       1200
CGTCGGAGCTGGCACCATCGGTGATTATGATAGTTGTGCTTGGCAATGTTTGGGGACTGG

      1210       1220       1230       1240       1250       1260
GCAGTTCCAACCTTTACTTGGTAGCCAGCCACATATTGGTAAGCTAAATGAGGTTGAATT

      1270       1280       1290       1300       1310       1320
CGTTGATGAGTTTAGAGTAGAAATGGTTTGTCGAGCAGAAAATGTAAGGGCAGCAATAAA

      1330       1340       1350       1360       1370       1380
TGCACTTATTGCTGCGCACCCTTATGAAGAACCTGCTTATCATATTCTGCAAACATTGAA

      1390       1400       1410       1420       1430       1440
TCTTGATGAGTTACCTTAAGTTAGATGCACTGCACTTAATTGGTTCGCTGTGCTAGGTTA

      1450       1460       1470       1480       1490       1500
GCAATTAGCAATTTTGACCATGTTAGCGATAGTTTTGGCACAAGTGATCGATATTAAACT

      1510       1520       1530       1540       1550       1560
ATCCGATTCAGATCCCATTTTTACTGCTGAATTAGGTTTCATTACACTTGTTCTAGTGGT

      1570       1580       1590       1600       1610       1620
TTTTCCCGACAGGTGTAACTCTGTTACTTGCGTAAGGTTGATAATCTCTACCGCATTGGC

      1630       1640       1650       1660       1670       1680
AGGAGTTACACCTGCACCAGGCATAATACTAATTCTACCATCTGCTTGGTTAACTAACGT

      1690       1700       1710       1720       1730       1740
TTGGATTAAGGCGCAGCCTTCTAGCGCTTGAGCTTGTTGACCAGAGGTTAAAATACGCTC

      1750       1760       1770       1780       1790       1800
ACAACCAGCAGTGATCAAGGTCTCCAAGGCTTGTTGTGGATCATTACACAAGTCGAAAGC

      1810       1820       1830       1840       1850       1860
GCGGTGGAAGGTTACGCCGAGATCACGTGATGCCACCATTAAGCGTTTTAAAGCTGGCTC

      1870       1880       1890       1900       1910       1920
GTCAATATTACCATCTGCTGTTAACGCGCCAATAACGACCCCTTGGACACCGAGTAACTT

      1930       1940       1950       1960       1970       1980
CATGAATTTGATGTCGGAAACCATAATATCAACTTCTTGTTCGCTATATACAAAATCACC

      1990       2000       2010       2020       2030       2040
GGCGCGAGGGCGAATAATGGCATAAATGGGGATCGTTGCTAGATCAATAGACTTTTGTAC

      2050       2060       2070       2080       2090       2100
AAAACCTGCGTTGGCGGTCAAGCCACCTAATGCTAATGCCGAGCACAACTCAATACGATC

      2110       2120       2130       2140       2150       2160
GGCGCCAGATGCTTGAGCCGTCAGCAGTGATTCTATATTATCGACACATACTTCTATTGT

      2170       2180       2190       2200       2210       2220
CATTGTCATATACTTCTCTTTAAAAAGTTTATTAAAAATAATAAAGCCAGCATAAGTCGT

      2230       2240       2250       2260       2270       2280
TTTATACAATATGAAAGGGGAAAAGGCGACTTAGCTCGCCTAGATCAATTATTATGGCAG
```

Fig. 5

```
      2290       2300       2310       2320       2330       2340
AATACTGCCGTATTGTGATTAGAAAGACAGTTTTTTAAGCTCAATAGCCGTTATCGCGTT

      2350       2360       2370       2380       2390       2400
GTTATCTACCATCGTGTAACTTTTCTGGCCTGGGTGCTTTATTAACACTGTTTCAGTGGC

      2410       2420       2430       2440       2450       2460
TGGATTAGGGTGAAATGATTCTTTTTTCAAATCTGTTTTTTTGTATTTGAACGTACCTGT

      2470       2480       2490       2500       2510       2520
AATGTCTTGCTGCTCACGAAGACGTACAAATATTGGTTGCGCATAGCTTGGTAGTGCCGC

      2530       2540       2550       2560       2570       2580
ATTGACATGTTGATAGAATTCAGACGCTGAAAATTCATGAATAGGGCAATTCAAAGTCAG

      2590       2600       2610       2620       2630       2640
CGCGACCATGCCTGCTCGGCCATCGTGATGTGGGAGCTTGACACCATAAGCCACACTTTG

      2650       2660       2670       2680       2690       2700
CTCAATTTGCACAAAATCGTTAACTTGAGCTTCTACTTGCGTCGTGGCGACATTTTCACC

      2710       2720       2730       2740       2750       2760
TTTCCAGCGGAATGTATCACCTAATCTATCCACAAAGGAAATATGGCGATAACCTTGGTA

      2770       2780       2790       2800       2810       2820
ATGAACGAGATCGCCGGTATTAAAATAACAGTCACCGTCTTTTAATACTGACTTAAATAG

      2830       2840       2850       2860       2870       2880
CTTTTTATTACTTTCGTTGTCATCGGTATAACCATCAAATGGTGAACGTTTAGTTATCTT

      2890       2900       2910       2920       2930       2940
TGTTAGCAGTAGCCCTGTTTCTCCCGTTTTTACTTTGGTCATTTTCCCTTTCGCATTATA

      2950       2960       2970       2980       2990       3000
CACAGGTTTGTCATTGTCAATATCATATTGTATGACGGTAAAAGCAAGTGGAGTAACCCC

      3010       3020       3030       3040       3050       3060
CGCTGTATGCGGTAAGTTCAGCGCATTGGAGAACACAAGATTACACTCACTGGCGCCATA

      3070       3080       3090       3100       3110       3120
GAATTCATTAATATGCTCGATCCCAAAACGTTGTTGGAAATGATCCCAAATTTCGGGGCG

      3130       3140       3150       3160       3170       3180
TAATCCATTACCTATGATTTTCTTTATATTATGCTGTTTGTCTTTATTGCTAGGCGGTAC

      3190       3200       3210       3220       3230       3240
ATTTAATAAATAACGGCAGAGCTCGCCGATGTAAGTAAACGCAGTGGCATTATGAGCACG

      3250       3260       3270       3280       3290       3300
AACTTCATCCCAAAAGCGACTTGAACTGAATTTTTCAGAAAGTGCGAGGGTTGCTGCGCT

      3310       3320       3330       3340       3350       3360
ACCAAACACGGCGCTTAATGACACTGTCAGTGCATTGTTATGGTATAGGGGGAGTGATAA

      3370       3380       3390       3400       3410       3420
ATACAATACATCATCAGCTGTTAAGCGTAATGATGCCATCCCCATGCCTGCCATGGATTT
```

Fig. 5

```
      3430       3440       3450       3460       3470       3480
AAACCAACGGTGATGGCTCATTCTTGCTGCTTTTGGCAGTCCAGTTTTTCCCGAGGTAAA

      3490       3500       3510       3520       3530       3540
GATATAAAACGCGCAATGCTTAAGCTGTATTTGTGCTGTTGATTCAGGGTTCAATACTGA

      3550       3560       3570       3580       3590       3600
ATATCCTGCGACTAGTGTAGATATGTTTTTATAACCATCACTCATGTCTGGCGTTTCTAA

      3610       3620       3630       3640       3650       3660
AGCGGGTACGTAAAAGACATTCTGTTGTAATGTCGATGACAAATTGGTTTCAATATTATT

      3670       3680       3690       3700       3710       3720
AATGGCGGATGTGTATAGTTCATCTGCGATGAGTAATTTGGTATCGACCACGCTAAGACT

      3730       3740       3750       3760       3770       3780
ATGTTCGAGGATTGAATCCCGTTGTGTCGTATTTATCATACAAGCAATCGCGCCAAGCTT

      3790       3800       3810       3820       3830       3840
GACAACTGCGAGGGCAATAATGATGGTTTCAGGCCTGTTATCGAGCATGATGGCGACTTT

      3850       3860       3870       3880       3890       3900
ATCATTTTTACCAATGCCGTATTCATGAAGGAAATGGGCATATTGATTTGCTTGCTTATT

      3910       3920       3930       3940       3950       3960
CAATGAATCGTAACTATAACGCTGGTCTTTAAATTGTATTGCGATCAAGTCAGAGTTATT

      3970       3980       3990       4000       4010       4020
GACAGCTTGCTGCTCTAGTAATAAACCAATAGACATAAAACGTTCGGGCTTTGCTTGTTG

      4030       4040       4050       4060       4070       4080
TAAGTGCCATAAGCCTTTGATGATTGGCTTTGGGGTTTTTAATAGATTGATGGTACTTTT

      4090       4100       4110       4120       4130       4140
CAGGAATTGTTTGCCGGTTATAACAGTCATAAGCTAATTCTTTTTATCAAGAAGAGGGGT

      4150       4160       4170       4180       4190       4200
TATGACACCAAATAAATGGGTCACGCGTTGGTTTAATTTGGTTAGACTAAATGTGTTGTT

      4210       4220       4230       4240       4250       4260
TTGCTGTGATAATGCGACGTTCAAACAAACTTGAGAAGGTAAAAAAATAGCATTTTTAAA

      4270       4280       4290       4300       4310       4320
TTGAACATCAATACTAATGTGTTGAATATCAATCAAGTTTTCTAACTGTGCGAGCACGCG

      4330       4340       4350       4360       4370       4380
TGCTTTAGCAAACATGCCATGTGCTATTGCTGTTTTAAACCCCATTAGTTTCGCTGGGAT

      4390       4400       4410       4420       4430       4440
AAAATGTAAATGGATTGGATTTGTGTCTTTGGAGATATAAGCATATTTATATACGTCAAA

      4450       4460       4470       4480       4490       4500
AGGACTAAATTTAAACAATGAAATCGGCTCGTAAGCATAATTCGCTGGCGTATTTACTAT

      4510       4520       4530       4540       4550       4560
TTTCTCACCGCTGGAACGTTGAGATCGTTGGCACGTTTTTCGCTGTTTCGTTTTCTGTAA
```

Fig. 5

```
      4570       4580       4590       4600       4610       4620
GAATGTCGATGTACACTCCCACGCAAATTGTCCATCTACAAACACATCAATATGAGTATC

      4630       4640       4650       4660       4670       4680
AATGAAACGTCCTGTATCCGTTATGTACTCCTTAATTACACGACATGTGCTCGTCAATAT

      4690       4700       4710       4720       4730       4740
CGCGTTTAATGCTATCGGTTGATGTTGTGTTATGCGATTTCGATAATGGACTAGTCCTAA

      4750       4760       4770       4780       4790       4800
TATAGATATCGGAAATTGTGTTGATGTCATGAGTTTCATCAATAATGGAAAGATCATCAC

      4810       4820       4830       4840       4850       4860
AAATGGATAAGTAACCGGTACATAGTTTGTGTTATTAAACCCACAGCATTTAATATATTG

      4870       4880       4890       4900       4910       4920
CTTTAAATTTCGCTGATCTATTTTTTGTCCACTGATACTAAATTGCTCAGTACACACTTG

      4930       4940       4950       4960       4970       4980
TGTCGACCAAGTGTTCATCAGTGTTTTAACAATTGTATTGACCACTGCTTTCACATATAA

      4990       5000       5010       5020       5030       5040
AAGCGAGATAATCGGTTGCTTTGTTAACAGTGTGATCTGGTTAGCGTGCATTGAAATAAT

      5050       5060       5070       5080       5090       5100
TCATATAAGAGTATGTAGCATTTATGTTAATATTTTGTTTTGGAAGTTGAATTGGCGAAT

      5110       5120       5130       5140       5150       5160
CCGTAATCGGTTTATGGCAGTTCGGTCAAATACTTCAGGTAAACTCGTTACTCATACCAT

      5170       5180       5190       5200       5210       5220
TGATAGTGTTAAAGTGATTGACTGAATAAAGAATAGAGCTAAAAGTGGAAAAATTATGCA

      5230       5240       5250       5260       5270       5280
AGATGCGGGTATGTTATTACGCATTGCTTATGAGGCAATGAAAGAGTTAGAGGTTGATGT

      5290       5300       5310       5320       5330       5340
CATTGAAGTACTTTCTCGTTGTAACATAAGTGAAGAAGTACTGAATGATAAGGATCTTCG

      5350       5360       5370       5380       5390       5400
CACACCTAATCATGCACAAACACATTTTTGGCAAGTATTAGAAGACATATCACAAGATCC

      5410       5420       5430       5440       5450       5460
TAACATCGGCATTTCACTTGGTGAGAGAATGCCAGTGTTCACGGGGCAGGTATTACAGTA

      5470       5480       5490       5500       5510       5520
TCTTTTTCTCAGTAGTCCTACATTTGGTACTGGCTGGGAACGCGCAACAAAATACTTTCG

      5530       5540       5550       5560       5570       5580
ATTAATCAGTGATGCGGCGAGTGTTTCTATCAAGATGGAAGGCTGTGAAGCGCGATTATC

      5590       5600       5610       5620       5630       5640
TGTGAACTTAGATGGTTTAGCGGAAGATGCGAATCGTCATTTGAATGATTGCCTAGTGAT

      5650       5660       5670       5680       5690       5700
CGGTGCATTTAAATTTTGTTTATATGTGACAGAAGGCGAATTTAAAGTAAGCAAAATAGC
```

Fig. 5

```
      5710       5720       5730       5740       5750       5760
CTTTGCTCATGCTCGCCCGAAAGATATTACTGCCTATACCAATGTATTTACATGTCCGAT

      5770       5780       5790       5800       5810       5820
TGAGTTTGCTGCCGAAGATAATTATATTTATTTCGATGCTGATTTACTCGAACGTCCTTC

      5830       5840       5850       5860       5870       5880
TTCGCATGCGGAGCCTGAGCTATTCGCCTTACACGATCAGCTTGCAAGCCGTAAAATAGC

      5890       5900       5910       5920       5930       5940
CAAGTTAGAACTGCAAGATTTAGTGGATAAAGTACGTAAGGTTATTGCACAACAACTTGA

      5950       5960       5970       5980       5990       6000
GTCTGGTGTGGTGACTTTAGAAAGTATCGCCACTGAACTTGACATGAAACCACGTATGCT

      6010       6020       6030       6040       6050       6060
AAGAGCGAAGTTAGCTGACATTGATTATAACTTTAATCAAATACTCGCTGATTTTCGTTG

      6070       6080       6090       6100       6110       6120
CGAGTTATCAAAAAAACTGTTGGCGAATACGGACGAGTCTATTGATCAGATTGTCTATCT

      6130       6140       6150       6160       6170       6180
CACTGGTTTTTCTGAACCAAGTACTTTTTATCGTGCCTTTAAGCGCTGGGTTAAAATGAC

      6190       6200       6210       6220       6230       6240
GCCAATTGAATATCGCCGTAGCAAACTCGCGGTTAGGCATGCTAATCAACACGAGTCCTA

      6250       6260       6270       6280       6290       6300
AAAATTCGCTGCTTAGTGCATAGTGCATAGTGCATAGTGCTAGTAAGCCAAGTACAAAGC

      6310       6320       6330       6340       6350       6360
GTTAAAGTTAAGTACTTGAGCGAACCATCAGACACCACTTACTAGATTAAGCACCTATTA

      6370       6380       6390       6400       6410       6420
ATGATTGACCACAAATTCTGATCGTATTGCCTGTGATCCCTGCAGCTTGAGGTTGCGCAA

      6430       6440       6450       6460       6470       6480
AAAAAGCTATCGCTTCAGCAACATCAACTGGCTTACCACCTTGTTTTAATGAATTCATAC

      6490       6500       6510       6520       6530       6540
GACGACCAGCTTCACGAACTGTAAATGGAATCGCTGCTGTCATTTTTGTTTCAATAAAGC

      6550       6560       6570       6580       6590       6600
CTGGTGCAACAGCATTAATGGTGATGTATTTGTCTGCAAGCGGAGTTTGCATTGCATCAA

      6610       6620       6630       6640       6650       6660
CATAACCAATGACTGCGGCCTTAGACGTTGCATAATTAGTCTGACCAAAGTTACCCGCAA

      6670       6680       6690       6700       6710       6720
TCCCACTCATCGAAGACACACAAACAATGCGGCCATAGTCGTTGAGCAGATCATCATTTA

      6730       6740       6750       6760       6770       6780
GCAGTCGCTCATTGATTCTTTCCATTGCCGACAAGTTAATATCCATCAGTACATCCCAAT

      6790       6800       6810       6820       6830       6840
GGTTATCCGGCATACGTGCTAGCGTTTTGTCTTTTGTTACCCCGGCATTATGGACGATGA
```

Fig. 5

```
      6850       6860       6870       6880       6890       6900
TATCAAGCGACTGTTCTCGCACAAAGTCAGCAATGATATTTGGGGCGTCAGCAGCGGTAA

      6910       6920       6930       6940       6950       6960
TATCAGCAACAATGCTGCTACCTTTCAAGCAATGAGCTACTTTTTCAAGGTCCTGTTTTA

      6970       6980       6990       7000       7010       7020
ATGCCGGAATGTCTAAGCAAATAACATGTGCGCCATCACGGGCGAGTGTTTCAGCAATAG

      7030       7040       7050       7060       7070       7080
CAGCCCCGATGCCACGTGATGCACCAGTGACAAGTGCTGTCTTTCCTTGTAATGGTTTTG

      7090       7100       7110       7120       7130       7140
CCGTGTTACTTGTTTCGTTAATAACTTCGTTAATAACTTCGTTAATAACTTCGTTAATAG

      7150       7160       7170       7180       7190       7200
CCCCATTAATCGAACCGGGTTTTACGTTAATAACCTGTGCTGAGATATAGGCTGATTTTG

      7210       7220       7230       7240       7250       7260
CTGAGGTTAAGAAACGTAGCGGGGCCTCTAATAATTGCTCACTACCAGGTTGTACATAGA

      7270       7280       7290       7300       7310       7320
TAAGTTGACAGGTACTACCATTCTTGCCTATTTCTTTGGCGACACTGCGACAAAACCCTT

      7330       7340       7350       7360       7370       7380
CTAAAGATCTTTGTACAGTCGCGTAGCTTACATCGTCAAGATGTTCACTCGGATGACCTA

      7390       7400       7410       7420       7430       7440
ACACGATCACTCTGCTGCATGGCGAGAGCTGCTTAATTACAGGTTGAAAAAAACGATGTA

      7450       7460       7470       7480       7490       7500
ATGCACTTAATTGCTTGCTGTTCTTAATGCCTGAGGCGTCGAAGATAATACCGTTGAAGC

      7510       7520       7530       7540       7550       7560
GATCTGTTTTAGCGATAGCATTAAGGCTAATAGGTGTCGCGACTAAAGACGTTTGATTAA

      7570       7580       7590       7600       7610       7620
ATTCAATATTAAGATCGGCTAACGCTGACGTGTTATTAGGATAAGAAATCGTGACTTCAG

      7630       7640       7650       7660       7670       7680
CATCTTTAAATGTGTTAAGAATGGGTTTAATTAATTTGCTGTTGCTGGCTGCGCCGATGA

      7690       7700       7710       7720       7730       7740
GTAAGTTGCCAGAGATGAGATCGGTTCCCTGATCGTAGCGTGTTAACGTAACCGGTCGTG

      7750       7760       7770       7780       7790       7800
GCAGATTAAGCGCTTTAAATAAACCTGATGTCCACTTGCCATTAGCGAGTTTTGCGTATG

      7810       7820       7830       7840       7850       7860
TATCCGTCATTTTCTAATCCTTGTTATAGTGAACAGTTTGAATCTCGAAGATGTACATGT

      7870       7880       7890       7900       7910       7920
GTTAAAAATTATCTGATAGCTATGACTTATCTGCCACTACGTAATAATAAATAGACCAGT

      7930       7940       7950       7960       7970       7980
TCATTACATCGTTAATCGATATAGTATAACTAAATACTAAGTAAATTATAATGATAAGAC
```

Fig. 5

M

```
      7990       8000       8010       8020       8030       8040
TGTTATCGTACTCGGATCAAACTCTGATCAGCAAATAATCAAATTAGAGTTTTTATTTTA

      8050       8060       8070       8080       8090       8100
AACTTGTATCAACAATGTTACATTAATGTATCTTACGTCTAATGTGCTACGGGCATATTT

      8110       8120       8130       8140       8150       8160
AAGTCACTAAATTAAAGGAATAAACCATGACAGGTCAAACAATAAGAAGAGTAGCAATTA

      8170       8180       8190       8200       8210       8220
TCGGCGGTAACCGTATCCCGTTTGCACGTTCAAATACAGCGTATTCAAAACTAAGTAACC

      8230       8240       8250       8260       8270       8280
AAGATATGCTGACGGAAACTATCCGTGGCTTGGTGGTTAAATATAACCTACGTGGTGAAC

      8290       8300       8310       8320       8330       8340
AACTGGGGGAAGTTGTTGCTGGTGCGGTAATTAAGCATTCTCGTGATTTTAACTTAACAC

      8350       8360       8370       8380       8390       8400
GTGAAGCCGTGCTAAGTGCAGGTCTTGCACCTGAAACGCCTTGTTATGACATTCAACAAG

      8410       8420       8430       8440       8450       8460
CTTGTGGTACTGGTCTAGCTGCAGCTATCCAAGTAGCAAACAAAATTGCGCTTGGTCAAA

      8470       8480       8490       8500       8510       8520
TAGAAGCGGGTATTGCTGGTGGTTCTGATACGACATCAGATGCACCGATTGCAGTCAGTG

      8530       8540       8550       8560       8570       8580
AAGGCATGCGTAGTGTATTACTTGAGCTTAATCGAGCTAAAACGGGTAAGCAACGTTTGA

      8590       8600       8610       8620       8630       8640
AAGCACTATCTCGTCTACGTCTAAAACACTTTGCGCCACTAACGCCTGCAAATAAAGAGC

      8650       8660       8670       8680       8690       8700
CGCGTACCAAAATGGCGATGGGCGATCATTGTCAAGTAACAGCGAAAGAGTGGAATATCT

      8710       8720       8730       8740       8750       8760
CACGTGAAGCACAAGATGCATTGGCCTGCGCAAGTCATCAAAAATTAGCTGCAGCATATG

      8770       8780       8790       8800       8810       8820
AAGAAGGTTTCTTTGATACGTTAGTTTCACCTATGGCCGGCTTAACGAAAGATAACGTAT

      8830       8840       8850       8860       8870       8880
TACGCGCAGATACAACAGTTGAGAAACTGGCTAAATTGAAACCTTGTTTTGATAAAGTAA

      8890       8900       8910       8920       8930       8940
ACGGCACTATGACGGCGGGTAACAGTACTAACCTTACCGATGGAGCATCAGCTGTATTAC

      8950       8960       8970       8980       8990       9000
TTGCAAGTGAAGAATGGGCAGCGGCACATAACTTACCAGTACAAGCTTATCTAACATTTG

      9010       9020       9030       9040       9050       9060
GTGAAACGGCCGCTATCGACTTCGTTGATAAGAAAGAAGGTCTGTTAATGGCGCCTGCAT

      9070       9080       9090       9100       9110       9120
ACGCAGTGCCAAAAATGTTGAAGCGTGCTGGCCTTACATTACAAGACTTCGATTACTATG
```

Fig. 5

```
      9130       9140       9150       9160       9170       9180
AAATACATGAAGCATTTGCTGCGCAGTTATTAGCAACGCTAGCAGCTTGGGAAGACGAAA

      9190       9200       9210       9220       9230       9240
AATTCTGTAAAGAAAAACTGGGTCTAGATGCTGCGCTTGGTTCAATTGATATGACCAAGT

      9250       9260       9270       9280       9290       9300
TAAACGTGAAAGGGAGTAGCTTAGCCACGGGTCACCCATTTGCCGCAACTGGTGGTCGTG

      9310       9320       9330       9340       9350       9360
TTGTCGCTACGCTAGCGCAATTACTTGATCAGAAAGGTTCAGGTCGTGGTTTGATCTCGA

      9370       9380       9390       9400       9410       9420
TTTGTGCTGCTGGTGGTCAAGGTATCACGGCAATTTTAGAGAAATAAACGCACTGTTTAT

      9430       9440       9450       9460       9470       9480
TATCTATTGATTAAGCTGTCCTGAGATACTGGATATTTTTAAATAAAACGCCAATACTGC

      9490       9500       9510       9520       9530       9540
AGAGTATTGGCGTTTTTTTGTAATACCAATTCCTATATAACGGTGCATTTTAAACACTTA

      9550       9560       9570       9580       9590       9600
ATTTCCGGCATTGGTATCATAAAAAAGCAGCACCGAAGTGCTGCTTGATTGTAGATTAAC

      9610       9620       9630       9640       9650       9660
CTATTAAAATAGAGAGGCTAGAATTAGTCTTCGTATGCTTCATTATGTACGCCAGCTGCA

      9670       9680       9690       9700       9710       9720
CGACCCGATGGATCAGCATTGTTTTGGAAACTTTCATCCCAAGCTAATGCTTCTACAGTT

      9730       9740       9750       9760       9770       9780
GAACAAGCAACGGATTTACCAAACGGTACGCATTTCGCTGCTGAATCACCTGGGAAGTGA

      9790       9800       9810       9820       9830       9840
TCTTCAAAGATGGCACGATAGTAGTAACCTTCTTTCGTATCTGGTGTGTTAATTGGGAAC

      9850       9860       9870       9880       9890       9900
TTAAATGCTGCACTTGCTAACATTTGATCAGTTACCGCTTCTTCAACGTGTACTTTAAGT

      9910       9920       9930       9940       9950       9960
TGGTCAATCCAAGAATAACCAACACCATCAGAGAATTGTTCTTTTTGACGCCATACAATT

      9970       9980       9990      10000      10010      10020
TCTTCAGGTAGTAAATCTTCAAATGCTTCTCGAATGATGTTTTTCTCAATGCGGTCGCCC

     10030      10040      10050      10060      10070      10080
GTGATCATTTTTAGTTCAGGGTTTAGACGCATTGACGCATCAACAAATTCTTTATCTAAG

     10090      10100      10110      10120      10130      10140
AAAGGAACACGTGCTTCGATGCCCCAAGCTGCCATAGATTTGTTTGCACGTAAGCAATCA

     10150      10160      10170      10180      10190      10200
AACATATGTAATTTATTTACTTTACGTACCGTCTCTTCATGGAATTCTTTCGCATTTGGC

     10210      10220      10230      10240      10250      10260
GCTTTGTGGAAGTACAAGTAACCACCGAACAGTTCATCAGCACCTTCACCAGAAAGCACC
```

Fig. 5

```
     10270      10280      10290      10300      10310      10320
ATCTTAATCCCCATGGCTTTAATTTTACGTGCCATTAGGTACATAGGGGTTGATGCACGA

     10330      10340      10350      10360      10370      10380
ATTGTTGTTACATCGTAGGTTTCAATGTGGTAAATCACGTCGCGTAAAGCGTCGATACCT

     10390      10400      10410      10420      10430      10440
TCTTGCACAGTAAATTCAATTGAATGATGGATAGTACCTAAGTGATCTGCCACTTTTTGT

     10450      10460      10470      10480      10490      10500
GCAGCGGCTAAATCTGGAGAACCATTTAGGCCTACAGAGAAAGAGTGTAGTTGTGGCCAC

     10510      10520      10530      10540      10550      10560
CATGCTTCGGTTTTACCACCGTCTTCAATACGACGTTTTGCATACTGTTGGGTGATTGCT

     10570      10580      10590      10600      10610      10620
GAAATAACAGATGAATCTAACCCGCCTGATAATAATACGCCGTAAGGTACATCACACATT

     10630      10640      10650      10660      10670      10680
AATTGACGTTTAACTGCATCTTCCAAACCTTGCTTAACAACGCTTTTATCACCACCATTT

     10690      10700      10710      10720      10730      10740
TGTGCAACGTTATCAAAATCTTTCCAATCACGTTGATAATAAGGCGTGACTACACCATCC

     10750      10760      10770      10780      10790      10800
TTACTCCACAGGTAATGACCTGCTGGGAATTCTTCAATTTGAGTACAAATTGGCACTAGT

     10810      10820      10830      10840      10850      10860
GCTTTCATTTCAGAGGCAACATAAAAGTTACCGTGTTCATCATAGCCCGTATAAAGAGGG

     10870      10880      10890      10900      10910      10920
ATGATACCGATATGGTCACGGCCAATCAGGTAAGCGTCCTCTGTTTCGTCATATAAAGCG

     10930      10940      10950      10960      10970      10980
AAAGCAAAAATACCATTTAGATCATCTAAAAATTGTGTGCCTTTTTCTTTATATAGCGCA

     10990      11000      11010      11020      11030      11040
AGTATCACTTCGCAATCTGATTCTGTTTGGAATTCAAAGTCTACGTTCAGCGTTTTCTTT

     11050      11060      11070      11080      11090      11100
AAATCTTTGTGGTTATAAATTTCACCATTAACAGCAAGTACGTGTGTCTTTTCTTCATTA

     11110      11120      11130      11140      11150      11160
TATAGCGGCTGTGCACCATTATTTACATCGACAATAGCAAGACGTTCATGAACTAAAATA

     11170      11180      11190      11200      11210      11220
GCATTGTCACTTGTATAGATACCTGACCAATCTGGGCCGCGGTGACGTAGTAACTTTGAT

     11230      11240      11250      11260      11270      11280
AGTTCTAGTGCTTGTTCGCGAAGAGGTTTAATGTCTGATTTGATGTCTAGAATTCCGAAT

     11290      11300      11310      11320      11330      11340
ATTGAGCACATAACTAATTCCTTCTGGGGCTGCGTCTGCAGCTAACTTTCTAAATAGTGT

     11350      11360      11370      11380      11390      11400
GTCTAATTTGCCACATTGTAGATTTAATGCAAACATTAATGATAAAACATTTATAAAAAA
```

Fig. 5

```
    11410      11420      11430      11440      11450      11460
TGTAATTCAATGTGGAATCGATAATTTAATGGCTTAAAAGTGAAGATCCATTAATTGTGA

    11470      11480      11490      11500      11510      11520
TGGCGAGGTGATAGACCAATGTAGACCTTAATGAATAAAGCAGGCACGATTGAATCCATT

    11530      11540      11550      11560      11570      11580
CAACGCAAAGTGGTACTAACTATTGTTTTAAACGTTATAAATAGTGTTTTAAAGGTTATA

    11590      11600      11610      11620      11630      11640
AGTAAATAATTTAAAAACAATAATAATCCACATGCATTAAATTTATCATGATAAACCGCT

    11650      11660      11670      11680      11690      11700
ATATCTCAATGGCAATTTGGGATAAGTGTAAAATATATGTAAAATGAATGAGTTGACTTG

    11710      11720      11730      11740      11750      11760
CTTTTTTTACACTAAGTGATGAAATTAAAGCTAGATGTCGTTGTTAGCATTGATTAATAA

    11770      11780      11790      11800      11810      11820
CGTACTAAAAATACGACATCTAGTATAGAAATTTAAAAAACAGTTGGTTTTGATAGCATAA

    11830      11840      11850      11860      11870      11880
CTGCATAAACTAATCAGCTTATTGTCTGTAATATTTTTGTAATTTAAATAGGTTTAATAA

    11890      11900      11910      11920      11930      11940
AATTATATGTCTGATAAATATAAACCGTACGACCTTTCCTTTAAAAAGACGTTTTTGCTG

    11950      11960      11970      11980      11990      12000
CCTAAGTTTTGGCCTGTGTGGTTCGGGGTGTTTGCAATATACTTATTAGCTTTTATGCCA

    12010      12020      12030      12040      12050      12060
GTAAAGCCGCGTGATAAATTTGCTCGATTCATAGCGAAGAAATTGTTTAGTCTAAAAATG

    12070      12080      12090      12100      12110      12120
ATGGCAAAGCGTAAAAAGGTAGCAAAGATCAATTTATCTATGTGCTTCCCTGAAATGGAT

    12130      12140      12150      12160      12170      12180
GATACGGAACAAGACCGTATAATCATGGTCAATCTAGTTACTTTTTGTCAAACTATCTTA

    12190      12200      12210      12220      12230      12240
AGTTATGCAGAGCCAAGTGCGCGTAGTCGTGCTTATAACCGTGACCGTATGATAGTGCAT

    12250      12260      12270      12280      12290      12300
GGTGGCGAGAATTTATTTCCGCTACTTGAACAAGGTAAGGCTTGTATCTTATTAGTGCCG

    12310      12320      12330      12340      12350      12360
CATAGCTTCGCTATTGATTTTGCAGGTTTACACATTGCTTCTTATGGCGCGCCATTTTGT

    12370      12380      12390      12400      12410      12420
ACTATGTTTAACAATTCTGAGAATGAGTTGTTCGATTGGCTGATGACACGTCAACGCGCT

    12430      12440      12450      12460      12470      12480
ATGTTTGGAGGCACTGTTTATCACCGCAAGGCAGGGCTAGGGGCTCTAGTTAAATCACTT

    12490      12500      12510      12520      12530      12540
AAGAGCGGTGAAAGCTGTTATTACTTACCTGATGAAGACCATGGACCTAAGCGTAGTGTA
```

Fig.5

```
     12550      12560      12570      12580      12590      12600
TTTGCGCCTTTATTTGCGACTCAAAAAGCAACTTTACCTGTAATGGGCAAGCTAGCAGAA

     12610      12620      12630      12640      12650      12660
AAAACAAATGCACTCGTTGTTCCTGTTTATGCGGCATATAATGAATCACTAGGTAAATTT

     12670      12680      12690      12700      12710      12720
GAAACCTTTATTCGACCAGCAATGCAAAACTTTCCATCAGAAAGCCCAGAACAAGATGCA

     12730      12740      12750      12760      12770      12780
GTGATGATGAATAAAGAGATTGAAGCCTTGATTGAATGTGGTGTTGATCAATATATGTGG

     12790      12800      12810      12820      12830      12840
ACACTTAGATTATTGAGAACACGTCCGGACGGTAAAAAAATCTACTAATAAAGTTTAATA

     12850      12860      12870      12880      12890      12900
AACACCATAATCTTCGTTGAATATGGTGTTTACCCCCCTGAATACCCTCTAAATTAATAA

     12910      12920      12930      12940      12950      12960
CAAAAAAAGCCATTTACGTAACATCTAATGATGATTTAGCCTGCACTTGCTTTGTTTTTA

     12970      12980      12990      13000      13010      13020
GTCTTAAGAGCCTAATAAACTTGATCTAGGTATAGATTCTGTCTTTCTTTACGTAACGCG

     13030      13040      13050      13060      13070      13080
ATCTATTTTTTTTAACCGATAGTTGTTATAATTAGTTTCATATGAAAGAGATATCGTTTC

     13090      13100      13110      13120      13130      13140
AGTAAAAGCTATTTCGTTTCAATAGATAATTTATTTATAGTCATATTTTCTGTAATGACA

     13150      13160      13170      13180      13190      13200
ATCATTTTCTCATCTAGACTATAGATAAGAATACGAATTAAGTAAGAACATTAATTTTAC

     13210      13220      13230      13240      13250      13260
AAGAATATAAAATATCCCATCGGAGCTATAAGAATGAAAAAGACTAAAATTGTTTGTACA

     13270      13280      13290      13300      13310      13320
ATTGGTCCAAAAACTGAATCAGTAGAGAAACTAACAGAGCTTGTTAATGCAGGCATGAAC

     13330      13340      13350      13360      13370      13380
GTTATGCGTTTAAATTTCTCTCATGGTAACTTTGCTGAACATTCAGTGCGTATTCAAAAT

     13390      13400      13410      13420      13430      13440
ATCCGTCAAGTAAGTGAAAACCTGAATAAGAAAATTGCTGTTTTACTGGATACTAAAGGT

     13450      13460      13470      13480      13490      13500
CCAGAAATCCGTACGATTAAACTAGAAAACGGTGACGATGTAATGTTGACCGCTGGTCAG

     13510      13520      13530      13540      13550      13560
TCATTCACGTTTACAACAGACATTAACGTGGTAGGTAATAAAGACTGTGTTGCTGTAACA

     13570      13580      13590      13600      13610      13620
TATGCTGGTTTTGCTAAAGACCTTAATCCTGGTGCAATCATCCTTGTTGATGATGGTTTA

     13630      13640      13650      13660      13670      13680
ATTGAAATGGAAGTTGTTGCAACAACTGACACTGAAGTTAAATGTACAGTATTAAATACT
```

Fig. 5

```
     13690      13700      13710      13720      13730      13740
GGTGCACTTGGTGAAAATAAAGGCGTTAACTTACCTAACATCAGTGTAGGTCTACCTGCA

     13750      13760      13770      13780      13790      13800
TTGTCAGAAAAAGATAAAGCTGATTTAGCGTTTGGTTGTGAGCAAGAAGTTGATTTTGTT

     13810      13820      13830      13840      13850      13860
GCTGCATCATTTATTCGTAAGGCTGATGATGTAAGAGAAATTCGTGAAATCCTATTTAAT

     13870      13880      13890      13900      13910      13920
AATGGTGGCGAAAACATTCAGATTATCTCGAAAATTGAAAACCAAGAAGGTGTAGACAAT

     13930      13940      13950      13960      13970      13980
TTCGATGAAATCTTAGCTGAATCAGACGGTATCATGGTTGCTCGTGGCGATCTCGGTGTT

     13990      14000      14010      14020      14030      14040
GAGATCCCAGTTGAAGAAGTGATCATGGCACAGAAGATGATGATCAAAAAATGTAATAAA

     14050      14060      14070      14080      14090      14100
GCAGGTAAAGTTGTAATTACTGCAACACAAATGCTTGATTCAATGATCAGTAACCCACGT

     14110      14120      14130      14140      14150      14160
CCAACACGTGCAGAAGCGGGCGATGTTGCCAATGCTGTGCTTGACGGTACCGACGCGGTA

     14170      14180      14190      14200      14210      14220
ATGCTTTCTGGTGAAACTGCGAAAGGTAAATACCCAGTTGAAGCTGTGTCTATCATGGCA

     14230      14240      14250      14260      14270      14280
AACATCTGTGAACGTACTGATAACTCAATGTCTTCGGATTTAGGTGCGAACATTGTTGCT

     14290      14300      14310      14320      14330      14340
AAAAGCATGCGCATTACAGAAGCTGTGTGTAAAGGTGCGGTAGAAACAACAGAAAAATTG

     14350      14360      14370      14380      14390      14400
TGTGCTCCACTTATTGTTGTTGCAACTCGTGGCGGTAAATCAGCAAAATCTGTTCGTAAA

     14410      14420      14430      14440      14450      14460
TACTTCCCGAAAGCAAATATTCTTGCTATCACAACAAATGAAAAAGCAGCGCAACAGTTA

     14470      14480      14490      14500      14510      14520
TGCCTAACTAAAGGCGTAAGCAGCTGCATCGTTGAGCAGATTGATAGCACTGATGAGTTC

     14530      14540      14550      14560      14570      14580
TACCGTAAAGGTAAAGAGCTTGCATTAGCAACTGGTTTAGCTAAAGAAGGCGATATCGTT

     14590      14600      14610      14620      14630      14640
GTTATGGTATCAGGTGCGTTAGTACCATCAGGTACAACGAATACGGCATCTGTTCACCAA

     14650      14660      14670      14680      14690      14700
CTTTAAGTTGCCATATTGATATTATAAAAAAGAGAGCGTATGCTCTCTTTTTTTATATCT

     14710      14720      14730      14740      14750      14760
GTAGTTTATATGTCTGTACAAAAAAATGATAAAGAGTACATAAACTATTAATATAGCGTA

     14770      14780      14790      14800      14810      14820
ATATATAATGATTAACGGTGATGAAAGGGTTAAATAAATGGATAGTGCTAAACATAAAAT
```

Fig. 5

```
     14830      14840      14850      14860      14870      14880
TGGCTTAGTCCTTTCTGGCGGTGGTGCGAAAGGTATTGCTCATCTTGGTGTATTAAAATA

     14890      14900      14910      14920      14930      14940
CCTGTTAGAGCAAGATATAAGACCGAATGTAATTGCGGGTACAAGTGCTGGCTCTATGGT

     14950      14960      14970      14980      14990      15000
TGGTGCACTTTATTGCTCAGGACTTGAGATTGATGACATTTTACAATTCTTCATCGATGT

     15010      15020      15030      15040      15050      15060
AAAACCTTTTTCTTGGAAGTTTACCCGTGCCCGTGCTGGCTTTATAGACCCGGCAAAATT

     15070      15080      15090      15100      15110      15120
ATATCCTGAAGTGCTAAAATATATCCCCGAGGATAGCTTTGAGTACCTTCAACCTGAATT

     15130      15140      15150      15160      15170      15180
GCGCATTGTTGCCACCAACATGTTACTCGGTAAAGAGCATATATTTAAAGATGGCTCCGT

     15190      15200      15210      15220      15230      15240
GATTAATGCCTTATTAGCATCAGCCAGCTACCCTTTAGTTTTTTCTCCGATGATCATTGA

     15250      15260      15270      15280      15290      15300
CGATCAAGTGTATTCAGATGGCGGTATTGTTAATCATTTCCCCGTGAGTGTCATTGAAGA

     15310      15320      15330      15340      15350      15360
TGATTGCGATAAAATAATCGGCGTATACGTGTCGCCCATTCGTCAGGTCGAAGCTGACGA

     15370      15380      15390      15400      15410      15420
ACTCTCGAGTATAAAAGACGTGGTATTACGTGCGTTCACGCTGCAGGGTAGTGGTGCTGA

     15430      15440      15450      15460      15470      15480
ATTAGATAAACTATCGCAATGTGATGTGCAAATTTATCCAGAAGCGCTATTGAATTACAA

     15490      15500      15510      15520      15530      15540
TACGTTTGCAACCGATGAAAAATCATTACGGGAGATCTACCAGATTGGTTATGATGCTGC

     15550      15560      15570      15580      15590      15600
AAAAGATCAACATGACAACCTTATGGCATTGAAAGAAAGTATCACCACCAGCGAGGTTAA

     15610      15620      15630      15640      15650      15660
AAAGAACGTCTTTAGCAAATGGTTTGGTGATAAACTTGCTAGCAACAGCGGCAAATAGCG

     15670      15680      15690      15700      15710      15720
GCCCACACGGATTTATACACTAGGATAATGGGCGTTAATAGCCTCACTGTCGTTGTGTGG

     15730      15740      15750      15760      15770      15780
TCTCTAATTTTAGCTAAATCTTGTGTTATACTGACTTCCTATTAATCATAAACGATTTAT

     15790      15800      15810      15820      15830      15840
CACGGTAAACATGACTCAAATAAATAACCCGCTTCACGGCATGACACTCGAAAAAGTAAT

     15850      15860      15870      15880      15890      15900
TAACAGTCTCGTTGAACAATATGGCTGGGATGGTCTTGGATACTACATCAACATTCGTTG

     15910      15920      15930      15940      15950      15960
CTTTACTGAAAATCCAAGTGTTAAGTCTAGTCTTAAATTTTTACGTAAAACCCCTTGGGC
```

Fig. 5

AM

```
     15970      15980      15990      16000      16010      16020
ACGTGATAAAGTAGAAGCGCTATATATCAAAATGGTGACTGAAGGCTAACTGTCTCCACG

     16030      16040      16050      16060      16070      16080
CTAGCGAACCGCTGTTTATAGTTAATATAAGTACTATAAGCAGGGCTCGTTAATTCAGTA

     16090      16100      16110      16120      16130      16140
TGTAATTAATCCTGAATACCTCCGCTTATTTCAACATTGTACTCTCTAGATAACACTCTC

     16150      16160      16170      16180      16190      16200
AACATTACACCTTCAACATCACAGCCTCCACATAACATCCGATGACATAGCCCTGTTATT

     16210      16220      16230      16240      16250      16260
TTTCACATTTATCTATATGCTATATATTTTAGCCATTTGATCAATTGAGTTAATTTCTGC

     16270      16280      16290      16300      16310      16320
AATGACAAAGATATACCATCATCCAGTACAAATTTATTATGAAGATACCGACCATTCTGG

     16330      16340      16350      16360      16370      16380
TGTTGTTTACCACCCTAACTTTTTAAAATACTTTGAACGTGCACGTGAGCATGTGATAAA

     16390      16400      16410      16420      16430      16440
TAGTGACTTACTAGCAACATTGTGGAATGAACGCGGTTTAGGTTTTGCGGTGTATAAAGC

     16450      16460      16470      16480      16490      16500
CAATATGACTTTTCAGGATGGGGTCGAATTTGCTGAAGTGTGTGATATTCGCACTTCTTT

     16510      16520      16530      16540      16550      16560
TGTCCTAGACGGTAAGTACAAAACGATCTGGCGCCAAGAAGTATGGCGTCCGAATGCGAC

     16570      16580      16590      16600      16610      16620
TAGGGCTGCCGTTATCGGTGATATTGAAATGGTGTGCTTAGACAAACAAAAACGTTTACA

     16630      16640      16650      16660      16670      16680
GCCCATCCCTGATGATGTGTTAGCTGCAATGGTTAGTGAATAAATGGTTCATGCATAAAT

     16690      16700      16710      16720      16730      16740
AGTTAATACATGATTCTGGCCCGTCACGTTTACAGATAAGAGGCATCCGATGCCTCCTTC

     16750      16760      16770      16780      16790      16800
CTATTACCAATACTACTGCTTATCCCTTTCTAACTATCTTTAGCGTCCATAACACACTGA

     16810      16820      16830      16840      16850      16860
GCATTTATTCTATTAATCAGTGATTGTGATTTAATTATCTTCTATATATGTAATTTAATG

     16870      16880      16890      16900      16910      16920
TAATTTTCAATTTATTTTTAGCTACATTAAGGCTTACGAATGTACGCTAAAATGAGATGT

     16930      16940      16950      16960      16970      16980
CAGACTAATTTTAGCTTATTAATCTGTTAGCCGTTTATATTTTATAAAGATGGGATTTAA

     16990      17000      17010      17020      17030      17040
CTTAAATGCAATTAATTATGGCGTAAATAGAGTGAAAACATGGCTAATATTCACTAAGTC

     17050      17060      17070      17080      17090      17100
CTGAATTTTATATAAAGTTTAATCTGTTATTTTAGCGTTTACCTGGTCTTATCAGTGAGG
```

Fig. 5

```
     17110      17120      17130      17140      17150      17160
TTTATAGCCATTATTAGTGGGATTGAAGTGATTTTTAAAGCTATGTATATTATTGCAAAT

     17170      17180      17190      17200      17210      17220
ATAAATTGTAACAATTAAGACTTTGGACACTTGAGTTCAATTTCGAATTGATTGGCATAA

     17230      17240      17250      17260      17270      17280
AATTTAAAACAGCTAAATCTACCTCAATCATTTTAGCAAATGTATGCAGGTAGATTTTTT

     17290      17300      17310      17320      17330      17340
TCGCCATTTAAGAGTACACTTGTACGCTAGGTTTTTGTTTAGTGTGCAAATGAACGTTTT

     17350      17360      17370      17380      17390      17400
GATGAGCATTGTTTTTAGAGCACAAAATAGATCCTTACAGGAGCAATAACGCAATGGCTA

     17410      17420      17430      17440      17450      17460
AAAAGAACACCACATCGATTAAGCACGCCAAGGATGTGTTAAGTAGTGATGATCAACAGT

     17470      17480      17490      17500      17510      17520
TAAATTCTCGCTTGCAAGAATGTCCGATTGCCATCATTGGTATGGCATCGGTTTTTGCAG

     17530      17540      17550      17560      17570      17580
ATGCTAAAAACTTGGATCAATTCTGGGATAACATCGTTGACTCTGTGGACGCTATTATTG

     17590      17600      17610      17620      17630      17640
ATGTGCCTAGCGATCGCTGGAACATTGACGACCATTACTCGGCTGATAAAAAAGCAGCTG

     17650      17660      17670      17680      17690      17700
ACAAGACATACTGCAAACGCGGTGGTTTCATTCCAGAGCTTGATTTTGATCCGATGGAGT

     17710      17720      17730      17740      17750      17760
TTGGTTTACCGCCAAATATCCTCGAGTTAACTGACATCGCTCAATTGTTGTCATTAATTG

     17770      17780      17790      17800      17810      17820
TTGCTCGTGATGTATTAAGTGATGCTGGCATTGGTAGTGATTATGACCATGATAAAATTG

     17830      17840      17850      17860      17870      17880
GTATCACGCTGGGTGTCGGTGGTGGTCAGAAACAAATTTCGCCATTAACGTCGCGCCTAC

     17890      17900      17910      17920      17930      17940
AAGGCCCGGTATTAGAAAAAGTATTAAAAGCCTCAGGCATTGATGAAGATGATCGCGCTA

     17950      17960      17970      17980      17990      18000
TGATCATCGACAAATTTAAAAAAGCCTACATCGGCTGGGAAGAGAACTCATTCCCAGGCA

     18010      18020      18030      18040      18050      18060
TGCTAGGTAACGTTATTGCTGGTCGTATCGCCAATCGTTTTGATTTTGGTGGTACTAACT

     18070      18080      18090      18100      18110      18120
GTGTGGTTGATGCGGCATGCGCTGGCTCCCTTGCAGCTGTTAAAATGGCGATCTCAGACT

     18130      18140      18150      18160      18170      18180
TACTTGAATATCGTTCAGAAGTCATGATATCGGGTGGTGTATGTTGTGATAACTCGCCAT

     18190      18200      18210      18220      18230      18240
TCATGTATATGTCATTCTCGAAAACACCAGCATTTACCACCAATGATGATATCCGTCCGT
```

Fig. 5

```
     18250      18260      18270      18280      18290      18300
TTGATGACGATTCAAAAGGCATGCTGGTTGGTGAAGGTATTGGCATGATGGCGTTTAAAC

     18310      18320      18330      18340      18350      18360
GTCTTGAAGATGCTGAACGTGACGGCGACAAAATTTATTCTGTACTGAAAGGTATCGGTA

     18370      18380      18390      18400      18410      18420
CATCTTCAGATGGTCGTTTCAAATCTATTTACGCTCCACGCCCAGATGGCCAAGCAAAAG

     18430      18440      18450      18460      18470      18480
CGCTAAAACGTGCTTATGAAGATGCCGGTTTTGCCCCTGAAACATGTGGTCTAATTGAAG

     18490      18500      18510      18520      18530      18540
GCCATGGTACGGGTACCAAAGCGGGTGATGCCGCAGAATTTGCTGGCTTGACCAAACACT

     18550      18560      18570      18580      18590      18600
TTGGCGCCGCCAGTGATGAAAAGCAATATATCGCCTTAGGCTCAGTTAAATCGCAAATTG

     18610      18620      18630      18640      18650      18660
GTCATACTAAATCTGCGGCTGGCTCTGCGGGTATGATTAAGGCGGCATTAGCGCTGCATC

     18670      18680      18690      18700      18710      18720
ATAAAATCTTACCTGCAACGATCCATATCGATAAACCAAGTGAAGCCTTGGATATCAAAA

     18730      18740      18750      18760      18770      18780
ACAGCCCGTTATACCTAAACAGCGAAACGCGTCCTTGGATGCCACGTGAAGATGGTATTC

     18790      18800      18810      18820      18830      18840
CACGTCGTGCAGGTATCAGCTCATTTGGTTTTGGCGGCACCAACTTCCATATTATTTTAG

     18850      18860      18870      18880      18890      18900
AAGAGTATCGCCCAGGTCACGATAGCGCATATCGCTTAAACTCAGTGAGCCAAACTGTGT

     18910      18920      18930      18940      18950      18960
TGATCTCGGCAAACGACCAACAAGGTATTGTTGCTGAGTTAAATAACTGGCGTACTAAAC

     18970      18980      18990      19000      19010      19020
TGGCTGTCGATGCTGATCATCAAGGGTTTGTATTTAATGAGTTAGTGACAACGTGGCCAT

     19030      19040      19050      19060      19070      19080
TAAAAACCCCATCCGTTAACCAAGCTCGTTTAGGTTTTGTTGCGCGTAATGCAAATGAAG

     19090      19100      19110      19120      19130      19140
CGATCGCGATGATTGATACGGCATTGAAACAATTCAATGCGAACGCAGATAAAATGACAT

     19150      19160      19170      19180      19190      19200
GGTCAGTACCTACCGGGGTTTACTATCGTCAAGCCGGTATTGATGCAACAGGTAAAGTGG

     19210      19220      19230      19240      19250      19260
TTGCGCTATTCTCAGGGCAAGGTTCGCAATACGTGAACATGGGTCGTGAATTAACCTGTA

     19270      19280      19290      19300      19310      19320
ACTTCCCAAGCATGATGCACAGTGCTGCGGCGATGGATAAAGAGTTCAGTGCCGCTGGTT

     19330      19340      19350      19360      19370      19380
TAGGCCAGTTATCTGCAGTTACTTTCCCTATCCCTGTTTATACGGATGCCGAGCGTAAGC
```

Fig. 5

```
     19390      19400      19410      19420      19430      19440
TACAAGAAGAGCAATTACGTTTAACGCAACATGCGCAACCAGCGATTGGTAGTTTGAGTG

     19450      19460      19470      19480      19490      19500
TTGGTCTGTTCAAAACGTTTAAGCAAGCAGGTTTTAAAGCTGATTTTGCTGCCGGTCATA

     19510      19520      19530      19540      19550      19560
GTTTCGGTGAGTTAACCGCATTATGGGCTGCCGATGTATTGAGCGAAAGCGATTACATGA

     19570      19580      19590      19600      19610      19620
TGTTAGCGCGTAGTCGTGGTCAAGCAATGGCTGCGCCAGAGCAACAAGATTTTGATGCAG

     19630      19640      19650      19660      19670      19680
GTAAGATGGCCGCTGTTGTTGGTGATCCAAAGCAAGTCGCTGTGATCATTGATACCCTTG

     19690      19700      19710      19720      19730      19740
ATGATGTCTCTATTGCTAACTTCAACTCGAATAACCAAGTTGTTATTGCTGGTACTACGG

     19750      19760      19770      19780      19790      19800
AGCAGGTTGCTGTAGCGGTTACAACCTTAGGTAATGCTGGTTTCAAAGTTGTGCCACTGC

     19810      19820      19830      19840      19850      19860
CGGTATCTGCTGCGTTCCATACACCTTTAGTTCGTCACGCGCAAAAACCATTTGCTAAAG

     19870      19880      19890      19900      19910      19920
CGGTTGATAGCGCTAAATTTAAAGCGCCAAGCATTCCAGTGTTTGCTAATGGCACAGGCT

     19930      19940      19950      19960      19970      19980
TGGTGCATTCAAGCAAACCGAATGACATTAAGAAAAACCTGAAAAACCACATGCTGGAAT

     19990      20000      20010      20020      20030      20040
CTGTTCATTTCAATCAAGAAATTGACAACATCTATGCTGATGGTGGCCGCGTATTTATCG

     20050      20060      20070      20080      20090      20100
AATTTGGTCCAAAGAATGTATTAACTAAATTGGTTGAAAACATTCTCACTGAAAAATCTG

     20110      20120      20130      20140      20150      20160
ATGTGACTGCTATCGCGGTTAATGCTAATCCTAAACAACCTGCGGACGTACAAATGCGCC

     20170      20180      20190      20200      20210      20220
AAGCTGCGCTGCAAATGGCAGTGCTTGGTGTCGCATTAGACAATATTGACCCGTACGACG

     20230      20240      20250      20260      20270      20280
CCGTTAAGCGTCCACTTGTTGCGCCGAAAGCATCACCAATGTTGATGAAGTTATCTGCAG

     20290      20300      20310      20320      20330      20340
CGTCTTATGTTAGTCCGAAAACGAAGAAAGCGTTTGCTGATGCATTGACTGATGGCTGGA

     20350      20360      20370      20380      20390      20400
CTGTTAAGCAAGCGAAAGCTGTACCTGCTGTTGTGTCACAACCACAAGTGATTGAAAAGA

     20410      20420      20430      20440      20450      20460
TCGTTGAAGTTGAAAAGATAGTTGAACGCATTGTCGAAGTAGAGCGTATTGTCGAAGTAG

     20470      20480      20490      20500      20510      20520
AAAAAATCGTCTACGTTAATGCTGACGGTTCGCTTATATCGCAAAATAATCAAGACGTTA
```

Fig. 5

```
     20530      20540      20550      20560      20570      20580
ACAGCGCTGTTGTTAGCAACGTGACTAATAGCTCAGTGACTCATAGCAGTGATGCTGACC

     20590      20600      20610      20620      20630      20640
TTGTTGCCTCTATTGAACGCAGTGTTGGTCAATTTGTTGCACACCAACAGCAATTATTAA

     20650      20660      20670      20680      20690      20700
ATGTACATGAACAGTTTATGCAAGGTCCACAAGACTACGCGAAAACAGTGCAGAACGTAC

     20710      20720      20730      20740      20750      20760
TTGCTGCGCAGACGAGCAATGAATTACCGGAAAGTTTAGACCGTACATTGTCTATGTATA

     20770      20780      20790      20800      20810      20820
ACGAGTTCCAATCAGAAACGCTACGTGTACATGAAACGTACCTGAACAATCAGACGAGCA

     20830      20840      20850      20860      20870      20880
ACATGAACACCATGCTTACTGGTGCTGAAGCTGATGTGCTAGCAACCCCAATAACTCAGG

     20890      20900      20910      20920      20930      20940
TAGTGAATACAGCCGTTGCCACTAGTCACAAGGTAGTTGCTCCAGTTATTGCTAATACAG

     20950      20960      20970      20980      20990      21000
TGACGAATGTTGTATCTAGTGTCAGTAATAACGCGGCGGTTGCAGTGCAAACTGTGGCAT

     21010      21020      21030      21040      21050      21060
TAGCGCCTACGCAAGAAATCGCTCCAACAGTCGCTACTACGCCAGCACCCGCATTGGTTG

     21070      21080      21090      21100      21110      21120
CTATCGTGGCTGAACCTGTGATTGTTGCGCATGTTGCTACAGAAGTTGCACCAATTACAC

     21130      21140      21150      21160      21170      21180
CATCAGTTACACCAGTTGTCGCAACTCAAGCGGCTATCGATGTAGCAACTATTAACAAAG

     21190      21200      21210      21220      21230      21240
TAATGTTAGAAGTTGTTGCTGATAAAACCGGTTATCCAACGGATATGCTGGAACTGAGCA

     21250      21260      21270      21280      21290      21300
TGGACATGGAAGCTGACTTAGGTATCGACTCAATCAAACGTGTTGAGATATTAGGCGCAG

     21310      21320      21330      21340      21350      21360
TACAGGAATTGATCCCTGACTTACCTGAACTTAATCCTGAAGATCTTGCTGAGCTACGCA

     21370      21380      21390      21400      21410      21420
CGCTTGGTGAGATTGTCGATTACATGAATTCAAAAGCCCAGGCTGTAGCTCCTACAACAG

     21430      21440      21450      21460      21470      21480
TACCTGTAACAAGTGCACCTGTTTCGCCTGCATCTGCTGGTATTGATTTAGCCCACATCC

     21490      21500      21510      21520      21530      21540
AAAACGTAATGTTAGAAGTGGTTGCAGACAAAACCGGTTACCCAACAGACATGCTAGAAC

     21550      21560      21570      21580      21590      21600
TGAGCATGGATATGGAAGCTGACTTAGGTATTGATTCAATCAAGCGTGTGGAAATCTTAG

     21610      21620      21630      21640      21650      21660
GTGCAGTACAGGAGATCATAACTGATTTACCTGAGCTAAACCCTGAAGATCTTGCTGAAT
```

Fig. 5

```
     21670      21680      21690      21700      21710      21720
TACGCACCCTAGGTGAAATCGTTAGTTACATGCAAAGCAAAGCGCCAGTCGCTGAAAGTG

     21730      21740      21750      21760      21770      21780
CGCCAGTGGCGACGGCTCCTGTAGCAACAAGCTCAGCACCGTCTATCGATTTGAACCACA

     21790      21800      21810      21820      21830      21840
TTCAAACAGTGATGATGGATGTAGTTGCAGATAAGACTGGTTATCCAACTGACATGCTAG

     21850      21860      21870      21880      21890      21900
AACTTGGCATGGACATGGAAGCTGATTTAGGTATCGATTCAATCAAACGTGTGGAAATAT

     21910      21920      21930      21940      21950      21960
TAGGCGCAGTGCAGGAGATCATCACTGATTTACCTGAGCTAAACCCAGAAGACCTCGCTG

     21970      21980      21990      22000      22010      22020
AATTACGCACGCTAGGTGAAATCGTTAGTTACATGCAAAGCAAAGCGCCAGTCGCTGAGA

     22030      22040      22050      22060      22070      22080
GTGCGCCAGTAGCGACGGCTTCTGTAGCAACAAGCTCTGCACCGTCTATCGATTTAAACC

     22090      22100      22110      22120      22130      22140
ATATCCAAACAGTGATGATGGAAGTGGTTGCAGACAAAACCGGTTATCCAGTAGACATGT

     22150      22160      22170      22180      22190      22200
TAGAACTTGCTATGGACATGGAAGCTGACCTAGGTATCGATTCAATCAAGCGTGTAGAAA

     22210      22220      22230      22240      22250      22260
TTTTAGGTGCGGTACAGGAAATCATTACTGACTTACCTGAGCTTAACCCTGAAGATCTTG

     22270      22280      22290      22300      22310      22320
CTGAACTACGTACATTAGGTGAAATCGTTAGTTACATGCAAAGCAAAGCGCCCGTAGCTG

     22330      22340      22350      22360      22370      22380
AAGCGCCTGCAGTACCTGTTGCAGTAGAAAGTGCACCTACTAGTGTAACAAGCTCAGCAC

     22390      22400      22410      22420      22430      22440
CGTCTATCGATTTAGACCACATCCAAAATGTAATGATGGATGTTGTTGCTGATAAGACTG

     22450      22460      22470      22480      22490      22500
GTTATCCTGCCAATATGCTTGAATTAGCAATGGACATGGAAGCCGACCTTGGTATTGATT

     22510      22520      22530      22540      22550      22560
CAATCAAGCGTGTTGAAATTCTAGGCGCGGTACAGGAGATCATTACTGATTTACCTGAAC

     22570      22580      22590      22600      22610      22620
TAAACCCAGAAGACTTAGCTGAACTACGTACGTTAGAAGAAATTGTAACCTACATGCAAA

     22630      22640      22650      22660      22670      22680
GCAAGGCGAGTGGTGTTACTGTAAATGTAGTGGCTAGCCCTGAAAATAATGCTGTATCAG

     22690      22700      22710      22720      22730      22740
ATGCATTTATGCAAAGCAATGTGGCGACTATCACAGCGGCCGCAGAACATAAGGCGGAAT

     22750      22760      22770      22780      22790      22800
TTAAACCGGCGCCGAGCGCAACCGTTGCTATCTCTCGTCTAAGCTCTATCAGTAAAATAA
```

Fig. 5

```
     22810      22820      22830      22840      22850      22860
GCCAAGATTGTAAAGGTGCTAACGCCTTAATCGTAGCTGATGGCACTGATAATGCTGTGT

     22870      22880      22890      22900      22910      22920
TACTTGCAGACCACCTATTGCAAACTGGCTGGAATGTAACTGCATTGCAACCAACTTGGG

     22930      22940      22950      22960      22970      22980
TAGCTGTAACAACGACGAAAGCATTTAATAAGTCAGTGAACCTGGTGACTTTAAATGGCG

     22990      23000      23010      23020      23030      23040
TTGATGAAACTGAAATCAACAACATTATTACTGCTAACGCACAATTGGATGCAGTTATCT

     23050      23060      23070      23080      23090      23100
ATCTGCACGCAAGTAGCGAAATTAATGCTATCGAATACCCACAAGCATCTAAGCAAGGCC

     23110      23120      23130      23140      23150      23160
TGATGTTAGCCTTCTTATTAGCGAAATTGAGTAAAGTAACTCAAGCCGCTAAAGTGCGTG

     23170      23180      23190      23200      23210      23220
GCGCCTTTATGATTGTTACTCAGCAGGGTGGTTCATTAGGTTTTGATGATATCGATTCTG

     23230      23240      23250      23260      23270      23280
CTACAAGTCATGATGTGAAAACAGACCTAGTACAAAGCGGCTTAAACGGTTTAGTTAAGA

     23290      23300      23310      23320      23330      23340
CACTGTCTCACGAGTGGGATAACGTATTCTGTCGTGCGGTTGATATTGCTTCGTCATTAA

     23350      23360      23370      23380      23390      23400
CGGCTGAACAAGTTGCAAGCCTTGTTAGTGATGAACTACTTGATGCTAACACTGTATTAA

     23410      23420      23430      23440      23450      23460
CAGAAGTGGGTTATCAACAAGCTGGTAAAGGCCTTGAACGTATCACGTTAACTGGTGTGG

     23470      23480      23490      23500      23510      23520
CTACTGACAGCTATGCATTAACAGCTGGCAATAACATCGATGCTAACTCGGTATTTTTAG

     23530      23540      23550      23560      23570      23580
TGAGTGGTGGCGCAAAAGGTGTAACTGCACATTGTGTTGCTCGTATAGCTAAAGAATATC

     23590      23600      23610      23620      23630      23640
AGTCTAAGTTCATCTTATTGGGACGTTCAACGTTCTCAAGTGACGAACCGAGCTGGGCAA

     23650      23660      23670      23680      23690      23700
GTGGTATTACTGATGAAGCGGCGTTAAAGAAAGCAGCGATGCAGTCTTTGATTACAGCAG

     23710      23720      23730      23740      23750      23760
GTGATAAACCAACACCCGTTAAGATCGTACAGCTAATCAAACCAATCCAAGCTAATCGTG

     23770      23780      23790      23800      23810      23820
AAATTGCGCAAACCTTGTCTGCAATTACCGCTGCTGGTGGCCAAGCTGAATATGTTTCTG

     23830      23840      23850      23860      23870      23880
CAGATGTAACTAATGCAGCAAGCGTACAAATGGCAGTCGCTCCAGCTATCGCTAAGTTCG

     23890      23900      23910      23920      23930      23940
GTGCAATCACTGGCATCATTCATGGCGCGGGTGTGTTAGCTGACCAATTCATTGAGCAAA
```

Fig. 5

```
     23950      23960      23970      23980      23990      24000
AAACACTGAGTGATTTTGAGTCTGTTTACAGCACTAAAATTGACGGTTTGTTATCGCTAC

     24010      24020      24030      24040      24050      24060
TATCAGTCACTGAAGCAAGCAACATCAAGCAATTGGTATTGTTCTCGTCAGCGGCTGGTT

     24070      24080      24090      24100      24110      24120
TCTACGGTAACCCCGGCCAGTCTGATTACTCGATTGCCAATGAGATCTTAAATAAAACCG

     24130      24140      24150      24160      24170      24180
CATACCGCTTTAAATCATTGCACCCACAAGCTCAAGTATTGAGCTTTAACTGGGGTCCTT

     24190      24200      24210      24220      24230      24240
GGGACGGTGGCATGGTAACGCCTGAGCTTAAACGTATGTTTGACCAACGTGGTGTTTACA

     24250      24260      24270      24280      24290      24300
TTATTCCACTTGATGCAGGTGCACAGTTATTGCTGAATGAACTAGCCGCTAATGATAACC

     24310      24320      24330      24340      24350      24360
GTTGTCCACAAATCCTCGTGGGTAATGACTTATCTAAAGATGCTAGCTCTGATCAAAAGT

     24370      24380      24390      24400      24410      24420
CTGATGAAAAGAGTACTGCTGTAAAAAAGCCACAAGTTAGTCGTTTATCAGATGCTTTAG

     24430      24440      24450      24460      24470      24480
TAACTAAAAGTATCAAAGCGACTAACAGTAGCTCTTTATCAAACAAGACTAGTGCTTTAT

     24490      24500      24510      24520      24530      24540
CAGACAGTAGTGCTTTTCAGGTTAACGAAAACCACTTTTTAGCTGACCACATGATCAAAG

     24550      24560      24570      24580      24590      24600
GCAATCAGGTATTACCAACGGTATGCGCGATTGCTTGGATGAGTGATGCAGCAAAAGCGA

     24610      24620      24630      24640      24650      24660
CTTATAGTAACCGAGACTGTGCATTGAAGTATGTCGGTTTCGAAGACTATAAATTGTTTA

     24670      24680      24690      24700      24710      24720
AAGGTGTGGTTTTTGATGGCAATGAGGCGGCGGATTACCAAATCCAATTGTCGCCTGTGA

     24730      24740      24750      24760      24770      24780
CAAGGGCGTCAGAACAGGATTCTGAAGTCCGTATTGCCGCAAAGATCTTTAGCCTGAAAA

     24790      24800      24810      24820      24830      24840
GTGACGGTAAACCTGTGTTTCATTATGCAGCGACAATATTGTTAGCAACTCAGCCACTTA

     24850      24860      24870      24880      24890      24900
ATGCTGTGAAGGTAGAACTTCCGACATTGACAGAAAGTGTTGATAGCAACAATAAAGTAA

     24910      24920      24930      24940      24950      24960
CTGATGAAGCACAAGCGTTATACAGCAATGGCACCTTGTTCCACGGTGAAAGTCTGCAGG

     24970      24980      24990      25000      25010      25020
GCATTAAGCAGATATTAAGTTGTGACGACAAGGGCCTGCTATTGGCTTGTCAGATAACCG

     25030      25040      25050      25060      25070      25080
ATGTTGCAACAGCTAAGCAGGGATCCTTCCCGTTAGCTGACAACAATATCTTTGCCAATG
```

Fig. 5

```
     25090      25100      25110      25120      25130      25140
ATTTGGTTTATCAGGCTATGTTGGTCTGGGTGCGCAAACAATTTGGTTTAGGTAGCTTAC

     25150      25160      25170      25180      25190      25200
CTTCGGTGACAACGGCTTGGACTGTGTATCGTGAAGTGGTTGTAGATGAAGTATTTTATC

     25210      25220      25230      25240      25250      25260
TGCAACTTAATGTTGTTGAGCATGATCTATTGGGTTCACGCGGCAGTAAAGCCCGTTGTG

     25270      25280      25290      25300      25310      25320
ATATTCAATTGATTGCTGCTGATATGCAATTACTTGCCGAAGTGAAATCAGCGCAAGTCA

     25330      25340      25350      25360      25370      25380
GTGTCAGTGACATTTTGAACGATATGTCATGATCGAGTAAATAATAACGATAGGCGTCAT

     25390      25400      25410      25420      25430      25440
GGTGAGCATGGCGTCTGCTTTCTTCATTTTTTAACATTAACAATATTAATAGCTAAACGC

     25450      25460      25470      25480      25490      25500
GGTTGCTTTAAACCAAGTAAACAAGTGCTTTTAGCTATTACTATTCCAAACAGGATATTA

     25510      25520      25530      25540      25550      25560
AAGAGAATATGACGGAATTAGCTGTTATTGGTATGGATGCTAAATTTAGCGGACAAGACA

     25570      25580      25590      25600      25610      25620
ATATTGACCGTGTGGAACGCGCTTTCTATGAAGGTGCTTATGTAGGTAATGTTAGCCGCG

     25630      25640      25650      25660      25670      25680
TTAGTACCGAATCTAATGTTATTAGCAATGGCGAAGAACAAGTTATTACTGCCATGACAG

     25690      25700      25710      25720      25730      25740
TTCTTAACTCTGTCAGTCTACTAGCGCAAACGAATCAGTTAAATATAGCTGATATCGCGG

     25750      25760      25770      25780      25790      25800
TGTTGCTGATTGCTGATGTAAAAAGTGCTGATGATCAGCTTGTAGTCCAAATTGCATCAG

     25810      25820      25830      25840      25850      25860
CAATTGAAAAACAGTGTGCGAGTTGTGTTGTTATTGCTGATTTAGGCCAAGCATTAAATC

     25870      25880      25890      25900      25910      25920
AAGTAGCTGATTTAGTTAATAACCAAGACTGTCCTGTGGCTGTAATTGGCATGAATAACT

     25930      25940      25950      25960      25970      25980
CGGTTAATTTATCTCGTCATGATCTTGAATCTGTAACTGCAACAATCAGCTTTGATGAAA

     25990      26000      26010      26020      26030      26040
CCTTCAATGGTTATAACAATGTAGCTGGGTTCGCGAGTTTACTTATCGCTTCAACTGCGT

     26050      26060      26070      26080      26090      26100
TTGCCAATGCTAAGCAATGTTATATATACGCCAACATTAAGGGCTTCGCTCAATCGGGCG

     26110      26120      26130      26140      26150      26160
TAAATGCTCAATTTAACGTTGGAAACATTAGCGATACTGCAAAGACCGCATTGCAGCAAG

     26170      26180      26190      26200      26210      26220
CTAGCATAACTGCAGAGCAGGTTGGTTTGTTAGAAGTGTCAGCAGTCGCTGATTCGGCAA
```

Fig. 5

```
     26230      26240      26250      26260.     26270      26280
TCGCATTGTCTGAAAGCCAAGGTTTAATGTCTGCTTATCATCATACGCAAACTTTGCATA

     26290      26300      26310      26320      26330      26340
CTGCATTAAGCAGTGCCCGTAGTGTGACTGGTGAAGGCGGGTGTTTTTCACAGGTCGCAG

     26350      26360      26370      26380      26390      26400
GTTTATTGAAATGTGTAATTGGTTTACATCAACGTTATATTCCGGCGATTAAAGATTGGC

     26410      26420      26430      26440      26450      26460
AACAACCGAGTGACAATCAAATGTCACGGTGGCGGAATTCACCATTCTATATGCCTGTAG

     26470      26480      26490      26500      26510      26520
ATGCTCGACCTTGGTTCCCACATGCTGATGGCTCTGCACACATTGCCGCTTATAGTTGTG

     26530      26540      26550      26560      26570      26580
TGACTGCTGACAGCTATTGTCATATTCTTTTACAAGAAAACGTCTTACAAGAACTTGTTT

     26590      26600      26610      26620      26630      26640
TGAAAGAAACAGTCTTGCAAGATAATGACTTAACTGAAAGCAAGCTTCAGACTCTTGAAC

     26650      26660      26670      26680      26690      26700
AAAACAATCCAGTAGCTGATCTGCGCACTAATGGTTACTTTGCATCGAGCGAGTTAGCAT

     26710      26720      26730      26740      26750      26760
TAATCATAGTACAAGGTAATGACGAAGCACAATTACGCTGTGAATTAGAAACTATTACAG

     26770      26780      26790      26800      26810      26820
GGCAGTTAAGTACTACTGGCATAAGTACTATCAGTATTAAACAGATCGCAGCAGACTGTT

     26830      26840      26850      26860      26870      26880
ATGCCCGTAATGATACTAACAAAGCCTATAGCGCAGTGCTTATTGCCGAGACTGCTGAAG

     26890      26900      26910      26920      26930      26940
AGTTAAGCAAAGAAATAACCTTGGCGTTTGCTGGTATCGCTAGCGTGTTTAATGAAGATG

     26950      26960      26970      26980      26990      27000
CTAAAGAATGGAAAACCCCGAAGGGCAGTTATTTTACCGCGCAGCCTGCAAATAAACAGG

     27010      27020      27030      27040      27050      27060
CTGCTAACAGCACACAGAATGGTGTCACCTTCATGTACCCAGGTATTGGTGCTACATATG

     27070      27080      27090      27100      27110      27120
TTGGTTTAGGGCGTGATCTATTTCATCTATTCCCACAGATTTATCAGCCTGTAGCGGCTT

     27130      27140      27150      27160      27170      27180
TAGCCGATGACATTGGCGAAAGTCTAAAAGATACTTTACTTAATCCACGCAGTATTAGTC

     27190      27200      27210      27220      27230      27240
GTCATAGCTTTAAAGAACTCAAGCAGTTGGATCTGGACCTGCGCGGTAACTTAGCCAATA

     27250      27260      27270      27280      27290      27300
TCGCTGAAGCCGGTGTGGGTTTTGCTTGTGTGTTTACCAAGGTATTTGAAGAAGTCTTTG

     27310      27320      27330      27340      27350      27360
CCGTTAAAGCTGACTTTGCTACAGGTTATAGCATGGGTGAAGTAAGCATGTATGCAGCAC
```

Fig. 5

```
    27370      27380      27390      27400      27410      27420
TAGGCTGCTGGCAGCAACCGGGATTGATGAGTGCTCGCCTTGCACAATCGAATACCTTTA

    27430      27440      27450      27460      27470      27480
ATCATCAACTTTGCGGCGAGTTAAGAACACTACGTCAGCATTGGGGCATGGATGATGTAG

    27490      27500      27510      27520      27530      27540
CTAACGGTACGTTCGAGCAGATCTGGGAAACCTATACCATTAAGGCAACGATTGAACAGG

    27550      27560      27570      27580      27590      27600
TCGAAATTGCCTCTGCAGATGAAGATCGTGTGTATTGCACCATTATCAATACACCTGATA

    27610      27620      27630      27640      27650      27660
GCTTGTTGTTAGCCGGTTATCCAGAAGCCTGTCAGCGAGTCATTAAGAATTTAGGTGTGC

    27670      27680      27690      27700      27710      27720
GTGCAATGGCATTGAATATGGCGAACGCAATTCACAGCGCGCCAGCTTATGCCGAATACG

    27730      27740      27750      27760      27770      27780
ATCATATGGTTGAGCTATACCATATGGATGTTACTCCACGTATTAATACCAAGATGTATT

    27790      27800      27810      27820      27830      27840
CAAGCTCATGTTATTTACCGATTCCACAACGCAGCAAAGCGATTTCCCACAGTATTGCTA

    27850      27860      27870      27880      27890      27900
AATGTTTGTGTGATGTGGTGGATTTCCCACGTTTGGTTAATACCTTACATGACAAAGGTG

    27910      27920      27930      27940      27950      27960
CGCGGGTATTCATTGAAATGGGTCCAGGTCGTTCGTTATGTAGCTGGGTAGATAAGATCT

    27970      27980      27990      28000      28010      28020
TAGTTAATGGCGATGGCGATAATAAAAAGCAAAGCCAACATGTATCTGTTCCTGTGAATG

    28030      28040      28050      28060      28070      28080
CCAAAGGCACCAGTGATGAACTTACTTATATTCGTGCGATTGCTAAGTTAATTAGTCATG

    28090      28100      28110      28120      28130      28140
GCGTGAATTTGAATTTAGATAGCTTGTTTAACGGGTCAATCCTGGTTAAAGCAGGCCATA

    28150      28160      28170      28180      28190      28200
TAGCAAACACGAACAAATAGTCAACATCGATATCTAGCGCTGGTGAGTTATACCTCATTA

    28210      28220      28230      28240      28250      28260
GTTGAAATATGGATTTAAAGAGAGTAATTATGGAAAATATTGCAGTAGTAGGTATTGCTA

    28270      28280      28290      28300      28310      28320
ATTTGTTCCCGGGCTCACAAGCACCGGATCAATTTTGGCAGCAATTGCTTGAACAACAAG

    28330      28340      28350      28360      28370      28380
ATTGCCGCAGTAAGGCGACCGCTGTTCAAATGGGCGTTGATCCTGCTAAATATACCGCCA

    28390      28400      28410      28420      28430      28440
ACAAAGGTGACACAGATAAATTTTACTGTGTGCACGGCGGTTACATCAGTGATTTCAATT

    28450      28460      28470      28480      28490      28500
TTGATGCTTCAGGTTATCAACTCGATAATGATTATTTAGCCGGTTTAGATGACCTTAATC
```

Fig. 5

```
     28510      28520      28530      28540      28550      28560
AATGGGGGCTTTATGTTACGAAACAAGCCCTTACCGATGCGGGTTATTGGGGCAGTACTG

     28570      28580      28590      28600      28610      28620
CACTAGAAAACTGTGGTGTGATTTTAGGTAATTTGTCATTCCCAACTAAATCATCTAATC

     28630      28640      28650      28660      28670      28680
AGCTGTTTATGCCTTTGTATCATCAAGTTGTTGATAATGCCTTAAAGGCGGTATTACATC

     28690      28700      28710      28720      28730      28740
CTGATTTTCAATTAACGCATTACACAGCACCGAAAAAAAACACATGCTGACAATGCATTAG

     28750      28760      28770      28780      28790      28800
TAGCAGGTTATCCAGCTGCATTGATCGCGCAAGCGGCGGGTCTTGGTGGTTCACATTTTG

     28810      28820      28830      28840      28850      28860
CACTGGATGCGGCTTGTGCTTCATCTTGTTATAGCGTTAAGTTAGCGTGTGATTACCTGC

     28870      28880      28890      28900      28910      28920
ATACGGGTAAAGCCAACATGATGCTTGCTGGTGCGGTATCTGCAGCAGATCCTATGTTCG

     28930      28940      28950      28960      28970      28980
TAAATATGGGTTTCTCGATATTCCAAGCTTACCCAGCTAACAATGTACATGCCCCGTTTG

     28990      29000      29010      29020      29030      29040
ACCAAAATTCACAAGGTCTATTTGCCGGTGAAGGCGCGGGCATGATGGTATTGAAACGTC

     29050      29060      29070      29080      29090      29100
AAAGTGATGCAGTACGTGATGGTGATCATATTTACGCCATTATTAAAGGCGGCGCATTAT

     29110      29120      29130      29140      29150      29160
CGAATGACGGTAAAGGCGAGTTTGTATTAAGCCCGAACACCAAGGGCCAAGTATTAGTAT

     29170      29180      29190      29200      29210      29220
ATGAACGTGCTTATGCCGATGCAGATGTTGACCCGAGTACAGTTGACTATATTGAATGTC

     29230      29240      29250      29260      29270      29280
ATGCAACGGGCACACCTAAGGGTGACAATGTTGAATTGCGTTCGATGGAAACCTTTTTCA

     29290      29300      29310      29320      29330      29340
GTCGCGTAAATAACAAACCATTACTGGGCTCGGTTAAATCTAACCTTGGTCATTTGTTAA

     29350      29360      29370      29380      29390      29400
CTGCCGCTGGTATGCCTGGCATGACCAAAGCTATGTTAGCGCTAGGTAAAGGTCTTATTC

     29410      29420      29430      29440      29450      29460
CTGCAACGATTAACTTAAAGCAACCACTGCAATCTAAAAACGGTTACTTTACTGGCGAGC

     29470      29480      29490      29500      29510      29520
AAATGCCAACGACGACTGTGTCTTGGCCAACAACTCCGGGTGCCAAGGCAGATAAACCGC

     29530      29540      29550      29560      29570      29580
GTACCGCAGGTGTGAGCGTATTTGGTTTTGGTGGCAGCAACGCCCATTTGGTATTACAAC

     29590      29600      29610      29620      29630      29640
AGCCAACGCAAACACTCGAGACTAATTTTAGTGTTGCTAAACCACGTGAGCCTTTGGCTA
```

Fig. 5

```
     29650      29660      29670      29680      29690      29700
TTATTGGTATGGACAGCCATTTTGGTAGTGCCAGTAATTTAGCGCAGTTCAAAACCTTAT

     29710      29720      29730      29740      29750      29760
TAAATAATAATCAAAATACCTTCCGTGAATTACCAGAACAACGCTGGAAAGGCATGGAAA

     29770      29780      29790      29800      29810      29820
GTAACGCTAACGTCATGCAGTCGTTACAATTACGCAAAGCGCCTAAAGGCAGTTACGTTG

     29830      29840      29850      29860      29870      29880
AACAGCTAGATATTGATTTCTTGCGTTTTAAAGTACCGCCTAATGAAAAAGATTGCTTGA

     29890      29900      29910      29920      29930      29940
TCCCGCAACAGTTAATGATGATGCAAGTGGCAGACAATGCTGCGAAAGACGGAGGTCTAG

     29950      29960      29970      29980      29990      30000
TTGAAGGTCGTAATGTTGCGGTATTAGTAGCGATGGGCATGGAACTGGAATTACATCAGT

     30010      30020      30030      30040      30050      30060
ATCGTGGTCGCGTTAATCTAACCACCCAAATTGAAGACAGCTTATTACAGCAAGGTATTA

     30070      30080      30090      30100      30110      30120
ACCTGACTGTTGAGCAACGTGAAGAACTGACCAATATTGCTAAAGACGGTGTTGCCTCGG

     30130      30140      30150      30160      30170      30180
CTGCACAGCTAAATCAGTATACGAGTTTCATTGGTAATATTATGGCGTCACGTATTTCGG

     30190      30200      30210      30220      30230      30240
CGTTATGGGATTTTTCTGGTCCTGCTATTACCGTATCGGCTGAAGAAAACTCTGTTTATC

     30250      30260      30270      30280      30290      30300
GTTGTGTTGAATTAGCTGAAAATCTATTTCAAACCAGTGATGTTGAAGCCGTTATTATTG

     30310      30320      30330      30340      30350      30360
CTGCTGTTGATTTGTCTGGTTCAATTGAAAACATTACTTTACGTCAGCACTACGGTCCAG

     30370      30380      30390      30400      30410      30420
TTAATGAAAAGGGATCTGTAAGTGAATGTGGTCCGGTTAATGAAAGCAGTTCAGTAACCA

     30430      30440      30450      30460      30470      30480
ACAATATTCTTGATCAGCAACAATGGCTGGTGGGTGAAGGCGCAGCGGCTATTGTCGTTA

     30490      30500      30510      30520      30530      30540
AACCGTCATCGCAAGTCACTGCTGAGCAAGTTTATGCGCGTATTGATGCGGTGAGTTTTG

     30550      30560      30570      30580      30590      30600
CCCCTGGTAGCAATGCGAAAGCAATTACGATTGCAGCGGATAAAGCATTAACACTTGCTG

     30610      30620      30630      30640      30650      30660
GTATCAGTGCTGCTGATGTAGCTAGTGTTGAAGCACATGCAAGTGGTTTTAGTGCCGAAA

     30670      30680      30690      30700      30710      30720
ATAATGCTGAAAAAACCGCGTTACCGACTTTATACCCAAGCGCAAGTATCAGTTCGGTGA

     30730      30740      30750      30760      30770      30780
AAGCCAATATTGGTCATACGTTTAATGCCTCGGGTATGGCGAGTATTATTAAAACGGCGC
```

Fig. 5

```
     30790      30800      30810      30820      30830      30840
TGCTGTTAGATCAGAATACGAGTCAAGATCAGAAAAGCAAACATATTGCTATTAACGGTC

     30850      30860      30870      30880      30890      30900
TAGGTCGTGATAACAGCTGCGCGCATCTTATCTTATCGAGTTCAGCGCAAGCGCATCAAG

     30910      30920      30930      30940      30950      30960
TTGCACCAGCGCCTGTATCTGGTATGGCCAAGCAACGCCCACAGTTAGTTAAAACCATCA

     30970      30980      30990      31000      31010      31020
AACTCGGTGGTCAGTTAATTAGCAACGCGATTGTTAACAGTGCGAGTTCATCTTTACACG

     31030      31040      31050      31060      31070      31080
CTATTAAAGCGCAGTTTGCCGGTAAGCACTTAAACAAAGTTAACCAGCCAGTGATGATGG

     31090      31100      31110      31120      31130      31140
ATAACCTGAAGCCCCAAGGTATTAGCGCTCATGCAACCAATGAGTATGTGGTGACTGGAG

     31150      31160      31170      31180      31190      31200
CTGCTAACACTCAAGCTTCTAACATTCAAGCATCTCATGTTCAAGCGTCAAGTCATGCAC

     31210      31220      31230      31240      31250      31260
AAGAGATAGCACCAAACCAAGTTCAAAATATGCAAGCTACAGCAGCCGCTGTAAGTTCAC

     31270      31280      31290      31300      31310      31320
CCCTTTCTCAACATCAACACACAGCGCAGCCCGTAGCGGCACCGAGCGTTGTTGGAGTGA

     31330      31340      31350      31360      31370      31380
CTGTGAAACATAAAGCAAGTAACCAAATTCATCAGCAAGCGTCTACGCATAAAGCATTTT

     31390      31400      31410      31420      31430      31440
TAGAAAGTCGTTTAGCTGCACAGAAAAACCTATCGCAACTTGTTGAATTGCAAACCAAGC

     31450      31460      31470      31480      31490      31500
TGTCAATCCAAACTGGTAGTGACAATACATCTAACAATACTGCGTCAACAAGCAATACAG

     31510      31520      31530      31540      31550      31560
TGCTAACAAATCCTGTATCAGCAACGCCATTAACACTTGTGTCTAATGCGCCTGTAGTAG

     31570      31580      31590      31600      31610      31620
CGACAAACCTAACCAGTACAGAAGCAAAAGCGCAAGCAGCTGCTACACAAGCTGGTTTTC

     31630      31640      31650      31660      31670      31680
AGATAAAAGGACCTGTTGGTTACAACTATCCACCGCTGCAGTTAATTGAACGTTATAATA

     31690      31700      31710      31720      31730      31740
AACCAGAAAACGTGATTTACGATCAAGCTGATTTGGTTGAATTCGCTGAAGGTGATATTG

     31750      31760      31770      31780      31790      31800
GTAAGGTATTTGGTGCTGAATACAATATTATTGATGGCTATTCGCGTCGTGTACGTCTGC

     31810      31820      31830      31840      31850      31860
CAACCTCAGATTACTTGTTAGTAACACGTGTTACTGAACTTGATGCCAAGGTGCATGAAT

     31870      31880      31890      31900      31910      31920
ACAAGAAATCATACATGTGTACTGAATATGATGTGCCTGTTGATGCACCGTTCTTAATTG
```

Fig. 5

```
     31930      31940      31950      31960      31970      31980
ATGGTCAGATCCCTTGGTCTGTTGCCGTCGAATCAGGCCAGTGTGATTTGATGTTGATTT

     31990      32000      32010      32020      32030      32040
CATATATCGGTATTGATTTCCAAGCGAAAGGCGAACGTGTTTACCGTTTACTTGATTGTG

     32050      32060      32070      32080      32090      32100
AATTAACTTTCCTTGAAGAGATGGCTTTTGGTGGCGATACTTTACGTTACGAGATCCACA

     32110      32120      32130      32140      32150      32160
TTGATTCGTATGCACGTAACGGCGAGCAATTATTATTCTTCTTCCATTACGATTGTTACG

     32170      32180      32190      32200      32210      32220
TAGGGGATAAGAAGGTACTTATCATGCGTAATGGTTGTGCTGGTTTCTTTACTGACGAAG

     32230      32240      32250      32260      32270      32280
AACTTTCTGATGGTAAAGGCGTTATTCATAACGACAAAGACAAAGCTGAGTTTAGCAATG

     32290      32300      32310      32320      32330      32340
CTGTTAAATCATCATTCACGCCGTTATTACAACATAACCGTGGTCAATACGATTATAACG

     32350      32360      32370      32380      32390      32400
ACATGATGAAGTTGGTTAATGGTGATGTTGCCAGTTGTTTTGGTCCGCAATATGATCAAG

     32410      32420      32430      32440      32450      32460
GTGGCCGTAATCCATCATTGAAATTCTCGTCTGAGAAGTTCTTGATGATTGAACGTATTA

     32470      32480      32490      32500      32510      32520
CCAAGATAGACCCAACCGGTGGTCATTGGGGACTAGGCCTGTTAGAAGGTCAGAAAGATT

     32530      32540      32550      32560      32570      32580
TAGACCCTGAGCATTGGTATTTCCCTTGTCACTTTAAAGGTGATCAAGTAATGGCTGGTT

     32590      32600      32610      32620      32630      32640
CGTTGATGTCGGAAGGTTGTGGCCAAATGGCGATGTTCTTCATGCTGTCTCTTGGTATGC

     32650      32660      32670      32680      32690      32700
ATACCAATGTGAACAACGCTCGTTTCCAACCACTACCAGGTGAATCACAAACGGTACGTT

     32710      32720      32730      32740      32750      32760
GTCGTGGGCAAGTACTGCCACAGCGCAATACCTTAACTTACCGTATGGAAGTTACTGCGA

     32770      32780      32790      32800      32810      32820
TGGGTATGCATCCACAGCCATTCATGAAAGCTAATATTGATATTTTGCTTGACGGTAAAG

     32830      32840      32850      32860      32870      32880
TGGTTGTTGATTTCAAAAACTTGAGCGTGATGATCAGCGAACAAGATGAGCATTCAGATT

     32890      32900      32910      32920      32930      32940
ACCCTGTAACACTGCCGAGTAATGTGGCGCTTAAAGCGATTACTGCACCTGTTGCGTCAG

     32950      32960      32970      32980      32990      33000
TAGCACCAGCATCTTCACCCGCTAACAGCGCGGATCTAGACGAACGTGGTGTTGAACCGT

     33010      33020      33030      33040      33050      33060
TTAAGTTTCCTGAACGTCCGTTAATGCGTGTTGAGTCAGACTTGTCTGCACCGAAAAGCA
```

Fig. 5

```
     33070      33080      33090      33100      33110      33120
AAGGTGTGACACCGATTAAGCATTTTGAAGCGCCTGCTGTTGCTGGTCATCATAGAGTGC

     33130      33140      33150      33160      33170      33180
CTAACCAAGCACCGTTTACACCTTGGCATATGTTTGAGTTTGCGACGGGTAATATTTCTA

     33190      33200      33210      33220      33230      33240
ACTGTTTCGGTCCTGATTTTGATGTTTATGAAGGTCGTATTCCACCTCGTACACCTTGTG

     33250      33260      33270      33280      33290      33300
GCGATTTACAAGTTGTTACTCAGGTTGTAGAAGTGCAGGGCGAACGTCTTGATCTTAAAA

     33310      33320      33330      33340      33350      33360
ATCCATCAAGCTGTGTAGCTGAATACTATGTACCGGAAGACGCTTGGTACTTTACTAAAA

     33370      33380      33390      33400      33410      33420
ACAGCCATGAAAACTGGATGCCTTATTCATTAATCATGGAAATTGCATTGCAACCAAATG

     33430      33440      33450      33460      33470      33480
GCTTTATTTCTGGTTACATGGGCACGACGCTTAAATACCCTGAAAAAGATCTGTTCTTCC

     33490      33500      33510      33520      33530      33540
GTAACCTTGATGGTAGCGGCACGTTATTAAAGCAGATTGATTTACGCGGCAAGACCATTG

     33550      33560      33570      33580      33590      33600
TGAATAAATCAGTCTTGGTTAGTACGGCTATTGCTGGTGGCGCGATTATTCAAAGTTTCA

     33610      33620      33630      33640      33650      33660
CGTTTGATATGTCTGTAGATGGCGAGCTATTTTATACTGGTAAAGCTGTATTTGGTTACT

     33670      33680      33690      33700      33710      33720
TTAGTGGTGAATCACTGACTAACCAACTGGGCATTGATAACGGTAAAACGACTAATGCGT

     33730      33740      33750      33760      33770      33780
GGTTTGTTGATAACAATACCCCCGCAGCGAATATTGATGTGTTTGATTTAACTAATCAGT

     33790      33800      33810      33820      33830      33840
CATTGGCTCTGTATAAAGCGCCTGTGGATAAACCGCATTATAAATTGGCTGGTGGTCAGA

     33850      33860      33870      33880      33890      33900
TGAACTTTATCGATACAGTGTCAGTGGTTGAAGGCGGTGGTAAAGCGGGCGTGGCTTATG

     33910      33920      33930      33940      33950      33960
TTTATGGCGAACGTACGATTGATGCTGATGATTGGTTCTTCCGTTATCACTTCCACCAAG

     33970      33980      33990      34000      34010      34020
ATCCGGTGATGCCAGGTTCATTAGGTGTTGAAGCTATTATTGAGTTGATGCAGACCTATG

     34030      34040      34050      34060      34070      34080
CGCTTAAAAATGATTTGGGTGGCAAGTTTGCTAACCCACGTTTCATTGCGCCGATGACGC

     34090      34100      34110      34120      34130      34140
AAGTTGATTGGAAATACCGTGGGCAAATTACGCCGCTGAATAAACAGATGTCACTGGACG

     34150      34160      34170      34180      34190      34200
TGCATATCACTGAGATCGTGAATGACGCTGGTGAAGTGCGAATCGTTGGTGATGCGAATC
```

Fig. 5

```
     34210      34220      34230      34240      34250      34260
TGTCTAAAGATGGTCTGCGTATTTATGAAGTTAAAAACATCGTTTTAAGTATTGTTGAAG

     34270      34280      34290      34300      34310      34320
CGTAAAGGGTCAAGTGTAACGTGCTTAAGCGCCGCATTGGTTAAAGACGCTTTGCACGCC

     34330      34340      34350      34360      34370      34380
GTGAATCCGTCCATGGAGGCTTGGGGTTGGCATCCATGCCAACAACAGCAAGCTTACTTT

     34390      34400      34410      34420      34430      34440
AATCAATACGGCTTGGTGTCCATTTAGACGCCTCGAACTTAGTAGTTAATAGACAAAATA

     34450      34460      34470      34480      34490      34500
ATTTAGCTGTGGAATGAATATAGTAAGTAATCATTCGGCAGCTACAAAAAAGGAATTAAG

     34510      34520      34530      34540      34550      34560
AATGTCGAGTTTAGGTTTTAACAATAACAACGCAATTAACTGGGCTTGGAAAGTAGATCC

     34570      34580      34590      34600      34610      34620
AGCGTCAGTTCATACACAAGATGCAGAAATTAAAGCAGCTTTAATGGATCTAACTAAACC

     34630      34640      34650      34660      34670      34680
TCTCTATGTGGCGAATAATTCAGGCGTAACTGGTATAGCTAATCATACGTCAGTAGCAGG

     34690      34700      34710      34720      34730      34740
TGCGATCAGCAATAACATCGATGTTGATGTATTGGCGTTTGCGCAAAAGTTAAACCCAGA

     34750      34760      34770      34780      34790      34800
AGATCTGGGTGATGATGCTTACAAGAAACAGCACGGCGTTAAATATGCTTATCATGGCGG

     34810      34820      34830      34840      34850      34860
TGCGATGGCAAATGGTATTGCCTCGGTTGAATTGGTTGTTGCGTTAGGTAAAGCAGGGCT

     34870      34880      34890      34900      34910      34920
GTTATGTTCATTTGGTGCTGCAGGTCTAGTGCCTGATGCGGTTGAAGATGCAATTCGTCG

     34930      34940      34950      34960      34970      34980
TATTCAAGCTGAATTACCAAATGGCCCTTATGCGGTTAACTTGATCCATGCACCAGCAGA

     34990      35000      35010      35020      35030      35040
AGAAGCATTAGAGCGTGGCGCGGTTGAACGTTTCCTAAAACTTGGCGTCAAGACGGTAGA

     35050      35060      35070      35080      35090      35100
GGCTTCAGCTTACCTTGGTTTAACTGAACACATTGTTTGGTATCGTGCTGCTGGTCTAAC

     35110      35120      35130      35140      35150      35160
TAAAAACGCAGATGGCAGTGTTAATATCGGTAACAAGGTTATCGCTAAAGTATCGCGTAC

     35170      35180      35190      35200      35210      35220
CGAAGTTGGTCGCCGCTTTATGGAACCTGCACCGCAAAAATTACTGGATAAGTTATTAGA

     35230      35240      35250      35260      35270      35280
ACAAAATAAGATCACCCCTGAACAAGCTGCTTTAGCGTTGCTTGTACCTATGGCTGATGA

     35290      35300      35310      35320      35330      35340
TATTACTGGGGAAGCGGATTCTGGTGGTCATACAGATAACCGTCCGTTTTTAACATTATT
```

Fig. 5

```
     35350      35360      35370      35380      35390      35400
ACCGACGATTATTGGTCTGCGTGATGAAGTGCAAGCGAAGTATAACTTCTCTCCTGCATT

     35410      35420      35430      35440      35450      35460
ACGTGTTGGTGCTGGTGGTGGTATCGGAACGCCTGAAGCAGCACTCGCTGCATTTAACAT

     35470      35480      35490      35500      35510      35520
GGGCGCGGCTTATATCGTTCTGGGTTCTGTGAATCAGGCGTGTGTTGAAGCGGGTGCATC

     35530      35540      35550      35560      35570      35580
TGAATATACTCGTAAACTGTTATCGACAGTTGAAATGGCTGATGTGACTATGGCACCTGC

     35590      35600      35610      35620      35630      35640
TGCAGATATGTTTGAAATGGGTGTGAAGCTGCAAGTATTAAAACGCGGTTCTATGTTCGC

     35650      35660      35670      35680      35690      35700
GATGCGTGCGAAGAAACTGTATGACTTGTATGTGGCTTATGACTCGATTGAAGATATCCC

     35710      35720      35730      35740      35750      35760
AGCTGCTGAACGTGAGAAGATTGAAAAACAAATCTTCCGTGCAAACCTAGACGAGATTTG

     35770      35780      35790      35800      35810      35820
GGATGGCACTATCGCTTTCTTTACTGAACGCGATCCAGAAATGCTAGCCCGTGCAACGAG

     35830      35840      35850      35860      35870      35880
TAGTCCTAAACGTAAAATGGCACTTATCTTCCGTTGGTATCTTGGCCTTTCTTCACGCTG

     35890      35900      35910      35920      35930      35940
GTCAAACACAGGCGAGAAGGGACGTGAAATGGATTATCAGATTTGGGCAGGCCCAAGTTT

     35950      35960      35970      35980      35990      36000
AGGTGCATTCAACAGCTGGGTGAAAGGTTCTTACCTTGAAGACTATACCCGCCGTGGCGC

     36010      36020      36030      36040      36050      36060
TGTAGATGTTGCTTTGCATATGCTTAAAGGTGCTGCGTATTTACAACGTGTAAACCAGTT

     36070      36080      36090      36100      36110      36120
GAAATTGCAAGGTGTTAGCTTAAGTACAGAATTGGCAAGTTATCGTACGAGTGATTAATG

     36130      36140      36150      36160      36170      36180
TTACTTGATGATATGTGAATTAATTAAAGCGCCTGAGGGCGCTTTTTTTGGTTTTTAACT

     36190      36200      36210      36220      36230      36240
CAGGTGTTGTAACTCGAAATTGCCCCTTTCAAGTTAGATCGATTACTCACTCACAATATG

     36250      36260      36270      36280      36290      36300
TTGATATCGCACTTGCCATATACTTGCTCATCCAAAGCCCTATATTGATAATGGTGTTAA

     36310      36320      36330      36340      36350      36360
TAGTCTTTAATATCCGAGTCTTTCTTCAGCATAATACTAATATAGAGACTCGACCAATGT

     36370      36380      36390      36400      36410      36420
TAAACACAACAAAGAATATATTCTTGTGTACTGCCTTATTATTAACGAGTGCGAGTACGA

     36430      36440      36450      36460      36470      36480
CAGCTACTACGCTAAACAATTCGATATCAGCAATTGAACAACGTATTTCTGGTCGTATCG
```

Fig. 5

```
     36490      36500      36510      36520      36530      36540
GTGTGGCTGTTTTAGATACGCAAAATAAACAAACGTGGGCTTACAATGGTGATGCACATT

     36550      36560      36570      36580      36590      36600
TTCCGATGATGAGTACATTCAAAACCCTCGCTTGCGCGAAAATGCTAAGTGAATCGACAA

     36610      36620      36630      36640      36650      36660
ATGGTAATCTGGATCCCAGTACTAGCTCATTGATAAAGGCTGAAGAATTAATCCCTTGGT

     36670      36680      36690      36700      36710      36720
CACCAGTCACTAAAACGTTTGTGAATAACACTATTACAGTGGCGAAAGCGTGTGAAGCAA

     36730      36740      36750      36760      36770      36780
CAATGCTGACCAGTGATAATACCGCGGCTAATATTGTTTTACAGTATATCGGAGGCCCTC

     36790      36800      36810      36820      36830      36840
AAGGCGTTACTGCATTCTTGCGAGAAATTGGTGATGAAGAGAGTCAGTTAGATCGTATAG

     36850      36860      36870      36880      36890      36900
AACCTGAATTGAATGAAGCTAAGGTCGGAGACTTGCGTGATACCACGACACCGAAAGCCA

     36910      36920      36930      36940      36950      36960
TAGTTACCACGCTCAACAAACTACTACTTGGTGATGTTCTACTTGATTTGGATAAAAACC

     36970      36980      36990      37000      37010      37020
AACTTAAAACATGGATGCAAAATAATAAAGTGTCAGATCCTTTACTGCGTTCTATATTAC

     37030      37040      37050      37060      37070      37080
CGCAAGGCTGGTTTATTGCCGACCGCTCAGGTGCGGGTGGTAATGGTTCTCGAGGTATAA

     37090      37100      37110      37120      37130      37140
CTGCTATGCTTTGGCACTCCGAGCGTCAACCGCTAATCATCAGTATTTATTTAACCGAAA

     37150      37160      37170      37180      37190      37200
CTGAGTTAGCAATGGCAATGCGCAATGAGATTATTGTTGAGATCGGTAAGCTGATATTCA

     37210      37220      37230      37240      37250      37260
AAGAATACGCGGTGAAATAATAAGTTATTTTTTGATAATACTTTAACGAGCGTAGCTATC

     37270      37280      37290      37300      37310      37320
GAAGTGAGGGCGTCAATTAGACACCTTTGCTTCCCCTACAAAATCTAATGTGTATTACCT

     37330      37340      37350      37360      37370      37380
CGGCTAGTACAATTGCCCTAAGTTATTTCTGTCCAGCTTTGGCTTAGTGCAATTGCGTTA

     37390      37400      37410      37420      37430      37440
GCCAATGTGAACACCAAGGGACTTTGTCGTACCATAACTACCAAGCGACTTTGTCGTTTT

     37450      37460      37470      37480      37490      37500
TATCTTTTCTTAGACAAACAGAGGTTAAATGAGTGACGCCTTCCAAATCACAGGAATGAA

     37510      37520      37530      37540      37550      37560
TCCGCATTTCAATAAAATCTAACCCGTACCAACTCCGTACAAGTTGATCTTTAGTTGTTT

     37570      37580      37590      37600      37610      37620
AAAATCTATAATAAATTCAATTACGGAATTAATCCGTACAACTGGAGGTTTTATGGCTAC
```

Fig. 5

```
    37630      37640      37650      37660      37670      37680
TGCAAGACTTGATATCCGTTTGGATGAAGAAATCAAAGCTAAGGCTGAGAAAGCATCAGC

    37690      37700      37710      37720      37730      37740
TTTACTCGGCTTAAAAAGTTTAACCGAATACGTTGTTCGCTTAATGGACGAAGATTCAAC

    37750      37760      37770      37780      37790      37800
TAAAGTAGTTTCTGAGCATGAGAGTATTACCGTTGAAGCGAATGTATTCGACCAATTTAT

    37810      37820      37830      37840      37850      37860
GGCTGCTTGTGATGAAGCGAAAGCCCCAAATAAAGCATTACTTGAAGCCGCTGTATTTAC

    37870      37880      37890      37900      37910      37920
TCAGAATGGTGAGTTTAAGTGAGTTATTCCAAACGTTTCAAAGAACTGGATAAATCAAAA

    37930      37940      37950      37960      37970      37980
CATGACAGAGCATCATTTGACTGTGGCGAAAAAGAGCTAAATGATTTTATCCAAACTCAA

    37990      38000      38010      38020      38030      38040
GCAGCCAAACATATGCAAGCAGGTATTAGCCGCACTCTGGTTTTACCTGCTTCTGCGCCG

    38050      38060      38070      38080      38090      38100
TTACCAAACAAAAAATATCCAATTTGCTCATTTTATAGTATCGCGCCAAGCTCAATTAGC

    38110      38120      38130      38140      38150      38160
CGCGATACGTTACCACAAGCAATGGCTAAAAAGTTACCACGTTATCCTATCCCTGTTTTT

    38170      38180      38190      38200      38210      38220
CTTTTGGCTCAACTTGCCGTCCATAAAGAGTTTCATGGGAGTGGGTTAGGCAAAGTTAGC

    38230      38240      38250      38260      38270      38280
TTAATTAAAGCGTTAGAGTACCTTTGGGAAATTAACTCTCACATGAGAGCTTACGCCATC

    38290      38300      38310      38320      38330      38340
GTTGTTGATTGTTTAACTGAACAAGCTGAGTCATTCTACGCTAAATATGGTTTCGACGTT

    38350      38360      38370      38380      38390      38400
CTCTGCGAAATAAATGGTCGAGTAAGAATGTTCATATCAATGAAAACAGTCAATCAGTTA

    38410      38420      38430      38440      38450      38460
TTCACTTAACAGTAAGAGTTAGTATAACAGTTGTATGAATTAAATTTATTATATTCGGTA

    38470      38480      38490      38500      38510      38520
ATCTCATTGCGATCACGCTAGAAGTGCGAGCGGGTCAGACCGAGGCCACAATAGCAGCCG

    38530      38540      38550      38560      38570      38580
TTACGTTTAGGGGATGACTTAAAAAGATAACTACTACGTCAGTGGCGATCCTAGAGGATT

    38590      38600      38610      38620      38630      38640
AAAGGTTTATGATTCACAACATTTATTTATTGTGCTTAATTTTTTCTATCCAATATGCGC

    38650      38660      38670      38680      38690      38700
AAGCTGTAAATATCACTGAAGTAGACTTTTATGTCAGTGATGATATCCCTAAAGATGTTG

    38710      38720      38730      38740      38750      38760
CCAAATTAAAGATAGGTGAATCCATAACGAACTCCAGCCTTATTCTAAGTAACTCATCTA
```

Fig. 5

```
     38770      38780      38790      38800      38810      38820
TTCCACTCTCGCGGGAGACGGGTAACATATATTACTCTTCATCAATTGCTAACTTGAACT

     38830      38840      38850      38860      38870      38880
ATGACTCGATAGAATTTGTTATGGCTCAATTGATGGCCGAAGATTCCAGCCTTTACAAGA

     38890      38900      38910      38920      38930      38940
TGCTGGTAAATAGCGATAGGTTGTCCGTGCTAGTAATGACATCTTCCCAGTCCACAGATC

     38950      38960      38970      38980      38990      39000
TCTATGGCTCGACTTACTCGGCTTATTTTCCTAATGTTGCGGTCATCGATTTGAATTGTG

     39010      39020      39030      39040      39050      39060
ACTCGCTAACTTTAGAACATGAGCTCGGCCATCTATACGGAGCTGAACATGAAGAAATAT

     39070      39080      39090      39100      39110      39120
ATGACGACTATGTCTTCTATGCTGCGATATGTGGAGACTATACGACTATCATGAACTCTA

     39130      39140      39150      39160      39170      39180
TGCAGCCTGAAATGAAAGAAAAACAAATGATAAAGGCATATTCATTCCCTGAATTAAAAG

     39190      39200      39210      39220      39230      39240
TGGATGGCTTGCAGTGCGGAAATGAAAATACGAATAACAAAAAGGTTATTTTAGACAATA

     39250      39260      39270      39280      39290      39300
TTGGTCGGTTTAGATAGGATTGGGATATTATTCTCATTCGGCTCTACTTAGTGCTGTTAT

     39310      39320      39330      39340      39350      39360
TATGAGTGCCAGTGCTTCTATCTACGATATTGGTCTTAACAAGTATTTATCTATAGACGC

     39370      39380      39390      39400      39410      39420
TAAGGTGTTATGTATTTAAGGGATGTTCAAGATGAAACTAGGTGTAAACGATGTATAGTT

     39430      39440      39450      39460      39470      39480
GTATAACATTTTTTCAACGGTTGGAACGTTCGATTCTATCGGGTAACAAGACCGCGACGA

     39490      39500      39510      39520      39530      39540
TCCGCGATAAGTCCGATAGTCATTACTTAGTTGGTCAGATGTTAGATGCTTGTACTCACG

     39550      39560      39570      39580      39590      39600
AAGATAATCGGAAAATGTGTCAAATAGAAATACTGAGCATTGAATATGTGACGTTTAGTG

     39610      39620      39630      39640      39650      39660
AATTAAACCGTGCGCACGCCAATGCTGAAGGTTTACCGTTTTTGTTTATGCTTAAGTGGA

     39670      39680      39690      39700      39710      39720
TAGTTCGAAAGATTTATCCGACTTCAAATGATTTATTTTTCATAAGTTTCAGAGTTGTAA

     39730      39740      39750      39760      39770      39780
CTATCGATATCTTATAAGTCTTAGTGCACAAAACAGAACTATTTATAGCGCTCAAGAAGG

     39790      39800      39810      39820      39830      39840
CGATAATTTGATAATGAATTATCGCCTTGTTACTATTAAGAGACTTTAAATGACTGAGAT

     39850      39860      39870      39880      39890      39900
ATAAGATATGACACGGAAGAACATATTGATCACAGGCGCAAGTTCAGGGTTGGGCCGAGG
```

Fig. 5

```
     39910      39920      39930      39940      39950      39960
TATGGCCATCGAATTTGCAAAATCAGGTCATAACTTAGCACTTTGTGCACGTAGACTTGA

     39970      39980      39990      40000      40010      40020
TAATTTAGTTGCACTGAAAGCAGAACTCTTAGCCCTCAATCCTCACATCCAAATCGAAAT

     40030      40040      40050      40060      40070      40080
AAAACCTCTTGATGTCAATGAACATGAACAAGTCTTCACTGTTTTCCATGAATTCAAAGC

     40090      40100      40110      40120      40130
TGAATTTGGTACGCTTGATCGTATTATTGTTAATGCTGGATTAGGCAAGGGTGGATCC
```

Fig. 5

```
        10         20         30         40         50         60
AAATGCAATTAATTATGGCGTAAATAGAGTGAAAACATGGCTAATATTCACTAAGTCCTG

        70         80         90        100        110        120
AATTTTATATAAAGTTTAATCTGTTATTTTAGCGTTTACCTGGTCTTATCAGTGAGGTTT

       130        140        150        160        170        180
ATAGCCATTATTAGTGGGATTGAAGTGATTTTTAAAGCTATGTATATTATTGCAAATATA

       190        200        210        220        230        240
AATTGTAACAATTAAGACTTTGGACACTTGAGTTCAATTTCGAATTGATTGGCATAAAAT

       250        260        270        280        290        300
TTAAAACAGCTAAATCTACCTCAATCATTTTAGCAAATGTATGCAGGTAGATTTTTTTCG

       310        320        330        340        350        360
CCATTTAAGAGTACACTTGTACGCTAGGTTTTTGTTTAGTGTGCAAATGAACGTTTTGAT

       370        380        390        400        410        420
GAGCATTGTTTTTAGAGCACAAAATAGATCCTTACAGGAGCAATAACGCAATGGCTAAAA

       430        440        450        460        470        480
AGAACACCACATCGATTAAGCACGCCAAGGATGTGTTAAGTAGTGATGATCAACAGTTAA

       490        500        510        520        530        540
ATTCTCGCTTGCAAGAATGTCCGATTGCCATCATTGGTATGGCATCGGTTTTTGCAGATG

       550        560        570        580        590        600
CTAAAAACTTGGATCAATTCTGGGATAACATCGTTGACTCTGTGGACGCTATTATTGATG

       610        620        630        640        650        660
TGCCTAGCGATCGCTGGAACATTGACGACCATTACTCGGCTGATAAAAAAGCAGCTGACA

       670        680        690        700        710        720
AGACATACTGCAAACGCGGTGGTTTCATTCCAGAGCTTGATTTTGATCCGATGGAGTTTG

       730        740        750        760        770        780
GTTTACCGCCAAATATCCTCGAGTTAACTGACATCGCTCAATTGTTGTCATTAATTGTTG

       790        800        810        820        830        840
CTCGTGATGTATTAAGTGATGCTGGCATTGGTAGTGATTATGACCATGATAAAATTGGTA

       850        860        870        880        890        900
TCACGCTGGGTGTCGGTGGTGGTCAGAAACAAATTTCGCCATTAACGTCGCGCCTACAAG

       910        920        930        940        950        960
GCCCGGTATTAGAAAAAGTATTAAAAGCCTCAGGCATTGATGAAGATGATCGCGCTATGA

       970        980        990       1000       1010       1020
TCATCGACAAATTTAAAAAAGCCTACATCGGCTGGGAAGAGAACTCATTCCCAGGCATGC

      1030       1040       1050       1060       1070       1080
TAGGTAACGTTATTGCTGGTCGTATCGCCAATCGTTTTGATTTTGGTGGTACTAACTGTG

      1090       1100       1110       1120       1130       1140
TGGTTGATGCGGCATGCGCTGGCTCCCTTGCAGCTGTTAAAATGGCGATCTCAGACTTAC
```

Fig. 6

```
      1150       1160       1170       1180       1190       1200
TTGAATATCGTTCAGAAGTCATGATATCGGGTGGTGTATGTTGTGATAACTCGCCATTCA

      1210       1220       1230       1240       1250       1260
TGTATATGTCATTCTCGAAAACACCAGCATTTACCACCAATGATGATATCCGTCCGTTTG

      1270       1280       1290       1300       1310       1320
ATGACGATTCAAAAGGCATGCTGGTTGGTGAAGGTATTGGCATGATGGCGTTTAAACGTC

      1330       1340       1350       1360       1370       1380
TTGAAGATGCTGAACGTGACGGCGACAAAATTTATTCTGTACTGAAAGGTATCGGTACAT

      1390       1400       1410       1420       1430       1440
CTTCAGATGGTCGTTTCAAATCTATTTACGCTCCACGCCCAGATGGCCAAGCAAAAGCGC

      1450       1460       1470       1480       1490       1500
TAAAACGTGCTTATGAAGATGCCGGTTTTGCCCCTGAAACATGTGGTCTAATTGAAGGCC

      1510       1520       1530       1540       1550       1560
ATGGTACGGGTACCAAAGCGGGTGATGCCGCAGAATTTGCTGGCTTGACCAAACACTTTG

      1570       1580       1590       1600       1610       1620
GCGCCGCCAGTGATGAAAAGCAATATATCGCCTTAGGCTCAGTTAAATCGCAAATTGGTC

      1630       1640       1650       1660       1670       1680
ATACTAAATCTGCGGCTGGCTCTGCGGGTATGATTAAGGCGGCATTAGCGCTGCATCATA

      1690       1700       1710       1720       1730       1740
AAATCTTACCTGCAACGATCCATATCGATAAACCAAGTGAAGCCTTGGATATCAAAAACA

      1750       1760       1770       1780       1790       1800
GCCCGTTATACCTAAACAGCGAAACGCGTCCTTGGATGCCACGTGAAGATGGTATTCCAC

      1810       1820       1830       1840       1850       1860
GTCGTGCAGGTATCAGCTCATTTGGTTTTGGCGGCACCAACTTCCATATTATTTTAGAAG

      1870       1880       1890       1900       1910       1920
AGTATCGCCCAGGTCACGATAGCGCATATCGCTTAAACTCAGTGAGCCAAACTGTGTTGA

      1930       1940       1950       1960       1970       1980
TCTCGGCAAACGACCAACAAGGTATTGTTGCTGAGTTAAATAACTGGCGTACTAAACTGG

      1990       2000       2010       2020       2030       2040
CTGTCGATGCTGATCATCAAGGGTTTGTATTTAATGAGTTAGTGACAACGTGGCCATTAA

      2050       2060       2070       2080       2090       2100
AAACCCCATCCGTTAACCAAGCTCGTTTAGGTTTTGTTGCGCGTAATGCAAATGAAGCGA

      2110       2120       2130       2140       2150       2160
TCGCGATGATTGATACGGCATTGAAACAATTCAATGCGAACGCAGATAAAATGACATGGT

      2170       2180       2190       2200       2210       2220
CAGTACCTACCGGGGTTTACTATCGTCAAGCCGGTATTGATGCAACAGGTAAAGTGGTTG

      2230       2240       2250       2260       2270       2280
CGCTATTCTCAGGGCAAGGTTCGCAATACGTGAACATGGGTCGTGAATTAACCTGTAACT
```

Fig. 6

```
      2290       2300       2310       2320       2330       2340
TCCCAAGCATGATGCACAGTGCTGCGGCGATGGATAAAGAGTTCAGTGCCGCTGGTTTAG

      2350       2360       2370       2380       2390       2400
GCCAGTTATCTGCAGTTACTTTCCCTATCCCTGTTTATACGGATGCCGAGCGTAAGCTAC

      2410       2420       2430       2440       2450       2460
AAGAAGAGCAATTACGTTTAACGCAACATGCGCAACCAGCGATTGGTAGTTTGAGTGTTG

      2470       2480       2490       2500       2510       2520
GTCTGTTCAAAACGTTTAAGCAAGCAGGTTTTAAAGCTGATTTTGCTGCCGGTCATAGTT

      2530       2540       2550       2560       2570       2580
TCGGTGAGTTAACCGCATTATGGGCTGCCGATGTATTGAGCGAAAGCGATTACATGATGT

      2590       2600       2610       2620       2630       2640
TAGCGCGTAGTCGTGGTCAAGCAATGGCTGCGCCAGAGCAACAAGATTTTGATGCAGGTA

      2650       2660       2670       2680       2690       2700
AGATGGCCGCTGTTGTTGGTGATCCAAAGCAAGTCGCTGTGATCATTGATACCCTTGATG

      2710       2720       2730       2740       2750       2760
ATGTCTCTATTGCTAACTTCAACTCGAATAACCAAGTTGTTATTGCTGGTACTACGGAGC

      2770       2780       2790       2800       2810       2820
AGGTTGCTGTAGCGGTTACAACCTTAGGTAATGCTGGTTTCAAAGTTGTGCCACTGCCGG

      2830       2840       2850       2860       2870       2880
TATCTGCTGCGTTCCATACACCTTTAGTTCGTCACGCGCAAAAACCATTTGCTAAAGCGG

      2890       2900       2910       2920       2930       2940
TTGATAGCGCTAAATTTAAAGCGCCAAGCATTCCAGTGTTTGCTAATGGCACAGGCTTGG

      2950       2960       2970       2980       2990       3000
TGCATTCAAGCAAACCGAATGACATTAAGAAAAACCTGAAAAACCACATGCTGGAATCTG

      3010       3020       3030       3040       3050       3060
TTCATTTCAATCAAGAAATTGACAACATCTATGCTGATGGTGGCCGCGTATTTATCGAAT

      3070       3080       3090       3100       3110       3120
TTGGTCCAAAGAATGTATTAACTAAATTGGTTGAAAACATTCTCACTGAAAAATCTGATG

      3130       3140       3150       3160       3170       3180
TGACTGCTATCGCGGTTAATGCTAATCCTAAACAACCTGCGGACGTACAAATGCGCCAAG

      3190       3200       3210       3220       3230       3240
CTGCGCTGCAAATGGCAGTGCTTGGTGTCGCATTAGACAATATTGACCCGTACGACGCCG

      3250       3260       3270       3280       3290       3300
TTAAGCGTCCACTTGTTGCGCCGAAAGCATCACCAATGTTGATGAAGTTATCTGCAGCGT

      3310       3320       3330       3340       3350       3360
CTTATGTTAGTCCGAAAACGAAGAAAGCGTTTGCTGATGCATTGACTGATGGCTGGACTG

      3370       3380       3390       3400       3410       3420
TTAAGCAAGCGAAAGCTGTACCTGCTGTTGTGTCACAACCACAAGTGATTGAAAAGATCG
```

Fig. 6

```
      3430       3440       3450       3460       3470       3480
TTGAAGTTGAAAAGATAGTTGAACGCATTGTCGAAGTAGAGCGTATTGTCGAAGTAGAAA

      3490       3500       3510       3520       3530       3540
AAATCGTCTACGTTAATGCTGACGGTTCGCTTATATCGCAAAATAATCAAGACGTTAACA

      3550       3560       3570       3580       3590       3600
GCGCTGTTGTTAGCAACGTGACTAATAGCTCAGTGACTCATAGCAGTGATGCTGACCTTG

      3610       3620       3630       3640       3650       3660
TTGCCTCTATTGAACGCAGTGTTGGTCAATTTGTTGCACACCAACAGCAATTATTAAATG

      3670       3680       3690       3700       3710       3720
TACATGAACAGTTTATGCAAGGTCCACAAGACTACGCGAAAACAGTGCAGAACGTACTTG

      3730       3740       3750       3760       3770       3780
CTGCGCAGACGAGCAATGAATTACCGGAAAGTTTAGACCGTACATTGTCTATGTATAACG

      3790       3800       3810       3820       3830       3840
AGTTCCAATCAGAAACGCTACGTGTACATGAAACGTACCTGAACAATCAGACGAGCAACA

      3850       3860       3870       3880       3890       3900
TGAACACCATGCTTACTGGTGCTGAAGCTGATGTGCTAGCAACCCCAATAACTCAGGTAG

      3910       3920       3930       3940       3950       3960
TGAATACAGCCGTTGCCACTAGTCACAAGGTAGTTGCTCCAGTTATTGCTAATACAGTGA

      3970       3980       3990       4000       4010       4020
CGAATGTTGTATCTAGTGTCAGTAATAACGCGGCGGTTGCAGTGCAAACTGTGGCATTAG

      4030       4040       4050       4060       4070       4080
CGCCTACGCAAGAAATCGCTCCAACAGTCGCTACTACGCCAGCACCCGCATTGGTTGCTA

      4090       4100       4110       4120       4130       4140
TCGTGGCTGAACCTGTGATTGTTGCGCATGTTGCTACAGAAGTTGCACCAATTACACCAT

      4150       4160       4170       4180       4190       4200
CAGTTACACCAGTTGTCGCAACTCAAGCGGCTATCGATGTAGCAACTATTAACAAAGTAA

      4210       4220       4230       4240       4250       4260
TGTTAGAAGTTGTTGCTGATAAAACCGGTTATCCAACGGATATGCTGGAACTGAGCATGG

      4270       4280       4290       4300       4310       4320
ACATGGAAGCTGACTTAGGTATCGACTCAATCAAACGTGTTGAGATATTAGGCGCAGTAC

      4330       4340       4350       4360       4370       4380
AGGAATTGATCCCTGACTTACCTGAACTTAATCCTGAAGATCTTGCTGAGCTACGCACGC

      4390       4400       4410       4420       4430       4440
TTGGTGAGATTGTCGATTACATGAATTCAAAAGCCCAGGCTGTAGCTCCTACAACAGTAC

      4450       4460       4470       4480       4490       4500
CTGTAACAAGTGCACCTGTTTCGCCTGCATCTGCTGGTATTGATTTAGCCCACATCCAAA

      4510       4520       4530       4540       4550       4560
ACGTAATGTTAGAAGTGGTTGCAGACAAAACCGGTTACCCAACAGACATGCTAGAACTGA
```

Fig. 6

```
      4570       4580       4590       4600       4610       4620
GCATGGATATGGAAGCTGACTTAGGTATTGATTCAATCAAGCGTGTGGAAATCTTAGGTG

      4630       4640       4650       4660       4670       4680
CAGTACAGGAGATCATAACTGATTTACCTGAGCTAAACCCTGAAGATCTTGCTGAATTAC

      4690       4700       4710       4720       4730       4740
GCACCCTAGGTGAAATCGTTAGTTACATGCAAAGCAAAGCGCCAGTCGCTGAAAGTGCGC

      4750       4760       4770       4780       4790       4800
CAGTGGCGACGGCTCCTGTAGCAACAAGCTCAGCACCGTCTATCGATTTGAACCACATTC

      4810       4820       4830       4840       4850       4860
AAACAGTGATGATGGATGTAGTTGCAGATAAGACTGGTTATCCAACTGACATGCTAGAAC

      4870       4880       4890       4900       4910       4920
TTGGCATGGACATGGAAGCTGATTTAGGTATCGATTCAATCAAACGTGTGGAAATATTAG

      4930       4940       4950       4960       4970       4980
GCGCAGTGCAGGAGATCATCACTGATTTACCTGAGCTAAACCCAGAAGACCTCGCTGAAT

      4990       5000       5010       5020       5030       5040
TACGCACGCTAGGTGAAATCGTTAGTTACATGCAAAGCAAAGCGCCAGTCGCTGAGAGTG

      5050       5060       5070       5080       5090       5100
CGCCAGTAGCGACGGCTTCTGTAGCAACAAGCTCTGCACCGTCTATCGATTTAAACCATA

      5110       5120       5130       5140       5150       5160
TCCAAACAGTGATGATGGAAGTGGTTGCAGACAAAACCGGTTATCCAGTAGACATGTTAG

      5170       5180       5190       5200       5210       5220
AACTTGCTATGGACATGGAAGCTGACCTAGGTATCGATTCAATCAAGCGTGTAGAAATTT

      5230       5240       5250       5260       5270       5280
TAGGTGCGGTACAGGAAATCATTACTGACTTACCTGAGCTTAACCCTGAAGATCTTGCTG

      5290       5300       5310       5320       5330       5340
AACTACGTACATTAGGTGAAATCGTTAGTTACATGCAAAGCAAAGCGCCCGTAGCTGAAG

      5350       5360       5370       5380       5390       5400
CGCCTGCAGTACCTGTTGCAGTAGAAAGTGCACCTACTAGTGTAACAAGCTCAGCACCGT

      5410       5420       5430       5440       5450       5460
CTATCGATTTAGACCACATCCAAAATGTAATGATGGATGTTGTTGCTGATAAGACTGGTT

      5470       5480       5490       5500       5510       5520
ATCCTGCCAATATGCTTGAATTAGCAATGGACATGGAAGCCGACCTTGGTATTGATTCAA

      5530       5540       5550       5560       5570       5580
TCAAGCGTGTTGAAATTCTAGGCGCGGTACAGGAGATCATTACTGATTTACCTGAACTAA

      5590       5600       5610       5620       5630       5640
ACCCAGAAGACTTAGCTGAACTACGTACGTTAGAAGAAATTGTAACCTACATGCAAAGCA

      5650       5660       5670       5680       5690       5700
AGGCGAGTGGTGTTACTGTAAATGTAGTGGCTAGCCCTGAAAATAATGCTGTATCAGATG
```

Fig. 6

```
      5710       5720       5730       5740       5750       5760
CATTTATGCAAAGCAATGTGGCGACTATCACAGCGGCCGCAGAACATAAGGCGGAATTTA

      5770       5780       5790       5800       5810       5820
AACCGGCGCCGAGCGCAACCGTTGCTATCTCTCGTCTAAGCTCTATCAGTAAAATAAGCC

      5830       5840       5850       5860       5870       5880
AAGATTGTAAAGGTGCTAACGCCTTAATCGTAGCTGATGGCACTGATAATGCTGTGTTAC

      5890       5900       5910       5920       5930       5940
TTGCAGACCACCTATTGCAAACTGGCTGGAATGTAACTGCATTGCAACCAACTTGGGTAG

      5950       5960       5970       5980       5990       6000
CTGTAACAACGACGAAAGCATTTAATAAGTCAGTGAACCTGGTGACTTTAAATGGCGTTG

      6010       6020       6030       6040       6050       6060
ATGAAACTGAAATCAACAACATTATTACTGCTAACGCACAATTGGATGCAGTTATCTATC

      6070       6080       6090       6100       6110       6120
TGCACGCAAGTAGCGAAATTAATGCTATCGAATACCCACAAGCATCTAAGCAAGGCCTGA

      6130       6140       6150       6160       6170       6180
TGTTAGCCTTCTTATTAGCGAAATTGAGTAAAGTAACTCAAGCCGCTAAAGTGCGTGGCG

      6190       6200       6210       6220       6230       6240
CCTTTATGATTGTTACTCAGCAGGGTGGTTCATTAGGTTTTGATGATATCGATTCTGCTA

      6250       6260       6270       6280       6290       6300
CAAGTCATGATGTGAAAACAGACCTAGTACAAAGCGGCTTAAACGGTTTAGTTAAGACAC

      6310       6320       6330       6340       6350       6360
TGTCTCACGAGTGGGATAACGTATTCTGTCGTGCGGTTGATATTGCTTCGTCATTAACGG

      6370       6380       6390       6400       6410       6420
CTGAACAAGTTGCAAGCCTTGTTAGTGATGAACTACTTGATGCTAACACTGTATTAACAG

      6430       6440       6450       6460       6470       6480
AAGTGGGTTATCAACAAGCTGGTAAAGGCCTTGAACGTATCACGTTAACTGGTGTGGCTA

      6490       6500       6510       6520       6530       6540
CTGACAGCTATGCATTAACAGCTGGCAATAACATCGATGCTAACTCGGTATTTTTAGTGA

      6550       6560       6570       6580       6590       6600
GTGGTGGCGCAAAAGGTGTAACTGCACATTGTGTTGCTCGTATAGCTAAAGAATATCAGT

      6610       6620       6630       6640       6650       6660
CTAAGTTCATCTTATTGGGACGTTCAACGTTCTCAAGTGACGAACCGAGCTGGGCAAGTG

      6670       6680       6690       6700       6710       6720
GTATTACTGATGAAGCGGCGTTAAAGAAAGCAGCGATGCAGTCTTTGATTACAGCAGGTG

      6730       6740       6750       6760       6770       6780
ATAAACCAACACCCGTTAAGATCGTACAGCTAATCAAACCAATCCAAGCTAATCGTGAAA

      6790       6800       6810       6820       6830       6840
TTGCGCAAACCTTGTCTGCAATTACCGCTGCTGGTGGCCAAGCTGAATATGTTTCTGCAG
```

Fig. 6

```
      6850       6860       6870       6880       6890       6900
ATGTAACTAATGCAGCAAGCGTACAAATGGCAGTCGCTCCAGCTATCGCTAAGTTCGGTG

      6910       6920       6930       6940       6950       6960
CAATCACTGGCATCATTCATGGCGCGGGTGTGTTAGCTGACCAATTCATTGAGCAAAAAA

      6970       6980       6990       7000       7010       7020
CACTGAGTGATTTTGAGTCTGTTTACAGCACTAAAATTGACGGTTTGTTATCGCTACTAT

      7030       7040       7050       7060       7070       7080
CAGTCACTGAAGCAAGCAACATCAAGCAATTGGTATTGTTCTCGTCAGCGGCTGGTTTCT

      7090       7100       7110       7120       7130       7140
ACGGTAACCCCGGCCAGTCTGATTACTCGATTGCCAATGAGATCTTAAATAAAACCGCAT

      7150       7160       7170       7180       7190       7200
ACCGCTTTAAATCATTGCACCCACAAGCTCAAGTATTGAGCTTTAACTGGGGTCCTTGGG

      7210       7220       7230       7240       7250       7260
ACGGTGGCATGGTAACGCCTGAGCTTAAACGTATGTTTGACCAACGTGGTGTTTACATTA

      7270       7280       7290       7300       7310       7320
TTCCACTTGATGCAGGTGCACAGTTATTGCTGAATGAACTAGCCGCTAATGATAACCGTT

      7330       7340       7350       7360       7370       7380
GTCCACAAATCCTCGTGGGTAATGACTTATCTAAAGATGCTAGCTCTGATCAAAAGTCTG

      7390       7400       7410       7420       7430       7440
ATGAAAAGAGTACTGCTGTAAAAAAGCCACAAGTTAGTCGTTTATCAGATGCTTTAGTAA

      7450       7460       7470       7480       7490       7500
CTAAAAGTATCAAAGCGACTAACAGTAGCTCTTTATCAAACAAGACTAGTGCTTTATCAG

      7510       7520       7530       7540       7550       7560
ACAGTAGTGCTTTTCAGGTTAACGAAAACCACTTTTTAGCTGACCACATGATCAAAGGCA

      7570       7580       7590       7600       7610       7620
ATCAGGTATTACCAACGGTATGCGCGATTGCTTGGATGAGTGATGCAGCAAAAGCGACTT

      7630       7640       7650       7660       7670       7680
ATAGTAACCGAGACTGTGCATTGAAGTATGTCGGTTTCGAAGACTATAAATTGTTTAAAG

      7690       7700       7710       7720       7730       7740
GTGTGGTTTTTGATGGCAATGAGGCGGCGGATTACCAAATCCAATTGTCGCCTGTGACAA

      7750       7760       7770       7780       7790       7800
GGGCGTCAGAACAGGATTCTGAAGTCCGTATTGCCGCAAAGATCTTTAGCCTGAAAAGTG

      7810       7820       7830       7840       7850       7860
ACGGTAAACCTGTGTTTCATTATGCAGCGACAATATTGTTAGCAACTCAGCCACTTAATG

      7870       7880       7890       7900       7910       7920
CTGTGAAGGTAGAACTTCCGACATTGACAGAAAGTGTTGATAGCAACAATAAAGTAACTG

      7930       7940       7950       7960       7970       7980
ATGAAGCACAAGCGTTATACAGCAATGGCACCTTGTTCCACGGTGAAAGTCTGCAGGGCA
```

Fig. 6

```
      7990       8000       8010       8020       8030       8040
TTAAGCAGATATTAAGTTGTGACGACAAGGGCCTGCTATTGGCTTGTCAGATAACCGATG

      8050       8060       8070       8080       8090       8100
TTGCAACAGCTAAGCAGGGATCCTTCCCGTTAGCTGACAACAATATCTTTGCCAATGATT

      8110       8120       8130       8140       8150       8160
TGGTTTATCAGGCTATGTTGGTCTGGGTGCGCAAACAATTTGGTTTAGGTAGCTTACCTT

      8170       8180       8190       8200       8210       8220
CGGTGACAACGGCTTGGACTGTGTATCGTGAAGTGGTTGTAGATGAAGTATTTTATCTGC

      8230       8240       8250       8260       8270       8280
AACTTAATGTTGTTGAGCATGATCTATTGGGTTCACGCGGCAGTAAAGCCCGTTGTGATA

      8290       8300       8310       8320       8330       8340
TTCAATTGATTGCTGCTGATATGCAATTACTTGCCGAAGTGAAATCAGCGCAAGTCAGTG

      8350       8360       8370       8380       8390       8400
TCAGTGACATTTTGAACGATATGTCATGATCGAGTAAATAATAACGATAGGCGTCATGGT

      8410       8420       8430       8440       8450       8460
GAGCATGGCGTCTGCTTTCTTCATTTTTTAACATTAACAATATTAATAGCTAAACGCGGT

      8470       8480       8490       8500       8510       8520
TGCTTTAAACCAAGTAAACAAGTGCTTTTAGCTATTACTATTCCAAACAGGATATTAAAG

      8530       8540       8550       8560       8570       8580
AGAATATGACGGAATTAGCTGTTATTGGTATGGATGCTAAATTTAGCGGACAAGACAATA

      8590       8600       8610       8620       8630       8640
TTGACCGTGTGGAACGCGCTTTCTATGAAGGTGCTTATGTAGGTAATGTTAGCCGCGTTA

      8650       8660       8670       8680       8690       8700
GTACCGAATCTAATGTTATTAGCAATGGCGAAGAACAAGTTATTACTGCCATGACAGTTC

      8710       8720       8730       8740       8750       8760
TTAACTCTGTCAGTCTACTAGCGCAAACGAATCAGTTAAATATAGCTGATATCGCGGTGT

      8770       8780       8790       8800       8810       8820
TGCTGATTGCTGATGTAAAAAGTGCTGATGATCAGCTTGTAGTCCAAATTGCATCAGCAA

      8830       8840       8850       8860       8870       8880
TTGAAAAACAGTGTGCGAGTTGTGTTGTTATTGCTGATTTAGGCCAAGCATTAAATCAAG

      8890       8900       8910       8920       8930       8940
TAGCTGATTTAGTTAATAACCAAGACTGTCCTGTGGCTGTAATTGGCATGAATAACTCGG

      8950       8960       8970       8980       8990       9000
TTAATTTATCTCGTCATGATCTTGAATCTGTAACTGCAACAATCAGCTTTGATGAAACCT

      9010       9020       9030       9040       9050       9060
TCAATGGTTATAACAATGTAGCTGGGTTCGCGAGTTTACTTATCGCTTCAACTGCGTTTG

      9070       9080       9090       9100       9110       9120
CCAATGCTAAGCAATGTTATATATACGCCAACATTAAGGGCTTCGCTCAATCGGGCGTAA
```

Fig. 6

```
      9130       9140       9150       9160       9170       9180
ATGCTCAATTTAACGTTGGAAACATTAGCGATACTGCAAAGACCGCATTGCAGCAAGCTA

      9190       9200       9210       9220       9230       9240
GCATAACTGCAGAGCAGGTTGGTTTGTTAGAAGTGTCAGCAGTCGCTGATTCGGCAATCG

      9250       9260       9270       9280       9290       9300
CATTGTCTGAAAGCCAAGGTTTAATGTCTGCTTATCATCATACGCAAACTTTGCATACTG

      9310       9320       9330       9340       9350       9360
CATTAAGCAGTGCCCGTAGTGTGACTGGTGAAGGCGGGTGTTTTTCACAGGTCGCAGGTT

      9370       9380       9390       9400       9410       9420
TATTGAAATGTGTAATTGGTTTACATCAACGTTATATTCCGGCGATTAAAGATTGGCAAC

      9430       9440       9450       9460       9470       9480
AACCGAGTGACAATCAAATGTCACGGTGGCGGAATTCACCATTCTATATGCCTGTAGATG

      9490       9500       9510       9520       9530       9540
CTCGACCTTGGTTCCCACATGCTGATGGCTCTGCACACATTGCCGCTTATAGTTGTGTGA

      9550       9560       9570       9580       9590       9600
CTGCTGACAGCTATTGTCATATTCTTTTACAAGAAAACGTCTTACAAGAACTTGTTTTGA

      9610       9620       9630       9640       9650       9660
AAGAAACAGTCTTGCAAGATAATGACTTAACTGAAAGCAAGCTTCAGACTCTTGAACAAA

      9670       9680       9690       9700       9710       9720
ACAATCCAGTAGCTGATCTGCGCACTAATGGTTACTTTGCATCGAGCGAGTTAGCATTAA

      9730       9740       9750       9760       9770       9780
TCATAGTACAAGGTAATGACGAAGCACAATTACGCTGTGAATTAGAAACTATTACAGGGC

      9790       9800       9810       9820       9830       9840
AGTTAAGTACTACTGGCATAAGTACTATCAGTATTAAACAGATCGCAGCAGACTGTTATG

      9850       9860       9870       9880       9890       9900
CCCGTAATGATACTAACAAAGCCTATAGCGCAGTGCTTATTGCCGAGACTGCTGAAGAGT

      9910       9920       9930       9940       9950       9960
TAAGCAAAGAAATAACCTTGGCGTTTGCTGGTATCGCTAGCGTGTTTAATGAAGATGCTA

      9970       9980       9990      10000      10010      10020
AAGAATGGAAAACCCCGAAGGGCAGTTATTTTACCGCGCAGCCTGCAAATAAACAGGCTG

     10030      10040      10050      10060      10070      10080
CTAACAGCACACAGAATGGTGTCACCTTCATGTACCCAGGTATTGGTGCTACATATGTTG

     10090      10100      10110      10120      10130      10140
GTTTAGGGCGTGATCTATTTCATCTATTCCCACAGATTTATCAGCCTGTAGCGGCTTTAG

     10150      10160      10170      10180      10190      10200
CCGATGACATTGGCGAAAGTCTAAAAGATACTTTACTTAATCCACGCAGTATTAGTCGTC

     10210      10220      10230      10240      10250      10260
ATAGCTTTAAAGAACTCAAGCAGTTGGATCTGGACCTGCGCGGTAACTTAGCCAATATCG
```

Fig. 6

```
     10270      10280      10290      10300      10310      10320
CTGAAGCCGGTGTGGGTTTTGCTTGTGTGTTTACCAAGGTATTTGAAGAAGTCTTTGCCG

     10330      10340      10350      10360      10370      10380
TTAAAGCTGACTTTGCTACAGGTTATAGCATGGGTGAAGTAAGCATGTATGCAGCACTAG

     10390      10400      10410      10420      10430      10440
GCTGCTGGCAGCAACCGGGATTGATGAGTGCTCGCCTTGCACAATCGAATACCTTTAATC

     10450      10460      10470      10480      10490      10500
ATCAACTTTGCGGCGAGTTAAGAACACTACGTCAGCATTGGGGCATGGATGATGTAGCTA

     10510      10520      10530      10540      10550      10560
ACGGTACGTTCGAGCAGATCTGGGAAACCTATACCATTAAGGCAACGATTGAACAGGTCG

     10570      10580      10590      10600      10610      10620
AAATTGCCTCTGCAGATGAAGATCGTGTGTATTGCACCATTATCAATACACCTGATAGCT

     10630      10640      10650      10660      10670      10680
TGTTGTTAGCCGGTTATCCAGAAGCCTGTCAGCGAGTCATTAAGAATTTAGGTGTGCGTG

     10690      10700      10710      10720      10730      10740
CAATGGCATTGAATATGGCGAACGCAATTCACAGCGCGCCAGCTTATGCCGAATACGATC

     10750      10760      10770      10780      10790      10800
ATATGGTTGAGCTATACCATATGGATGTTACTCCACGTATTAATACCAAGATGTATTCAA

     10810      10820      10830      10840      10850      10860
GCTCATGTTATTTACCGATTCCACAACGCAGCAAAGCGATTTCCCACAGTATTGCTAAAT

     10870      10880      10890      10900      10910      10920
GTTTGTGTGATGTGGTGGATTTCCCACGTTTGGTTAATACCTTACATGACAAAGGTGCGC

     10930      10940      10950      10960      10970      10980
GGGTATTCATTGAAATGGGTCCAGGTCGTTCGTTATGTAGCTGGGTAGATAAGATCTTAG

     10990      11000      11010      11020      11030      11040
TTAATGGCGATGGCGATAATAAAAAGCAAAGCCAACATGTATCTGTTCCTGTGAATGCCA

     11050      11060      11070      11080      11090      11100
AAGGCACCAGTGATGAACTTACTTATATTCGTGCGATTGCTAAGTTAATTAGTCATGGCG

     11110      11120      11130      11140      11150      11160
TGAATTTGAATTTAGATAGCTTGTTTAACGGGTCAATCCTGGTTAAAGCAGGCCATATAG

     11170      11180      11190      11200      11210      11220
CAAACACGAACAAATAGTCAACATCGATATCTAGCGCTGGTGAGTTATACCTCATTAGTT

     11230      11240      11250      11260      11270      11280
GAAATATGGATTTAAAGAGAGTAATTATGGAAAATATTGCAGTAGTAGGTATTGCTAATT

     11290      11300      11310      11320      11330      11340
TGTTCCCGGGCTCACAAGCACCGGATCAATTTTGGCAGCAATTGCTTGAACAACAAGATT

     11350      11360      11370      11380      11390      11400
GCCGCAGTAAGGCGACCGCTGTTCAAATGGGCGTTGATCCTGCTAAATATACCGCCAACA
```

Fig. 6

```
     11410      11420      11430      11440      11450      11460
AAGGTGACACAGATAAATTTTACTGTGTGCACGGCGGTTACATCAGTGATTTCAATTTTG

     11470      11480      11490      11500      11510      11520
ATGCTTCAGGTTATCAACTCGATAATGATTATTTAGCCGGTTTAGATGACCTTAATCAAT

     11530      11540      11550      11560      11570      11580
GGGGGCTTTATGTTACGAAACAAGCCCTTACCGATGCGGGTTATTGGGGCAGTACTGCAC

     11590      11600      11610      11620      11630      11640
TAGAAAACTGTGGTGTGATTTTAGGTAATTTGTCATTCCCAACTAAATCATCTAATCAGC

     11650      11660      11670      11680      11690      11700
TGTTTATGCCTTTGTATCATCAAGTTGTTGATAATGCCTTAAAGGCGGTATTACATCCTG

     11710      11720      11730      11740      11750      11760
ATTTTCAATTAACGCATTACACAGCACCGAAAAAAACACATGCTGACAATGCATTAGTAG

     11770      11780      11790      11800      11810      11820
CAGGTTATCCAGCTGCATTGATCGCGCAAGCGGCGGGTCTTGGTGGTTCACATTTTGCAC

     11830      11840      11850      11860      11870      11880
TGGATGCGGCTTGTGCTTCATCTTGTTATAGCGTTAAGTTAGCGTGTGATTACCTGCATA

     11890      11900      11910      11920      11930      11940
CGGGTAAAGCCAACATGATGCTTGCTGGTGCGGTATCTGCAGCAGATCCTATGTTCGTAA

     11950      11960      11970      11980      11990      12000
ATATGGGTTTCTCGATATTCCAAGCTTACCCAGCTAACAATGTACATGCCCCGTTTGACC

     12010      12020      12030      12040      12050      12060
AAAATTCACAAGGTCTATTTGCCGGTGAAGGCGCGGGCATGATGGTATTGAAACGTCAAA

     12070      12080      12090      12100      12110      12120
GTGATGCAGTACGTGATGGTGATCATATTTACGCCATTATTAAAGGCGGCGCATTATCGA

     12130      12140      12150      12160      12170      12180
ATGACGGTAAAGGCGAGTTTGTATTAAGCCCGAACACCAAGGGCCAAGTATTAGTATATG

     12190      12200      12210      12220      12230      12240
AACGTGCTTATGCCGATGCAGATGTTGACCCGAGTACAGTTGACTATATTGAATGTCATG

     12250      12260      12270      12280      12290      12300
CAACGGGCACACCTAAGGGTGACAATGTTGAATTGCGTTCGATGGAAACCTTTTTCAGTC

     12310      12320      12330      12340      12350      12360
GCGTAAATAACAAACCATTACTGGGCTCGGTTAAATCTAACCTTGGTCATTTGTTAACTG

     12370      12380      12390      12400      12410      12420
CCGCTGGTATGCCTGGCATGACCAAAGCTATGTTAGCGCTAGGTAAAGGTCTTATTCCTG

     12430      12440      12450      12460      12470      12480
CAACGATTAACTTAAAGCAACCACTGCAATCTAAAAACGGTTACTTTACTGGCGAGCAAA

     12490      12500      12510      12520      12530      12540
TGCCAACGACGACTGTGTCTTGGCCAACAACTCCGGGTGCCAAGGCAGATAAACCGCGTA
```

Fig. 6

```
     12550      12560      12570      12580      12590      12600
CCGCAGGTGTGAGCGTATTTGGTTTTGGTGGCAGCAACGCCCATTTGGTATTACAACAGC

     12610      12620      12630      12640      12650      12660
CAACGCAAACACTCGAGACTAATTTTAGTGTTGCTAAACCACGTGAGCCTTTGGCTATTA

     12670      12680      12690      12700      12710      12720
TTGGTATGGACAGCCATTTTGGTAGTGCCAGTAATTTAGCGCAGTTCAAAACCTTATTAA

     12730      12740      12750      12760      12770      12780
ATAATAATCAAAATACCTTCCGTGAATTACCAGAACAACGCTGGAAAGGCATGGAAAGTA

     12790      12800      12810      12820      12830      12840
ACGCTAACGTCATGCAGTCGTTACAATTACGCAAAGCGCCTAAAGGCAGTTACGTTGAAC

     12850      12860      12870      12880      12890      12900
AGCTAGATATTGATTTCTTGCGTTTTAAAGTACCGCCTAATGAAAAAGATTGCTTGATCC

     12910      12920      12930      12940      12950      12960
CGCAACAGTTAATGATGATGCAAGTGGCAGACAATGCTGCGAAAGACGGAGGTCTAGTTG

     12970      12980      12990      13000      13010      13020
AAGGTCGTAATGTTGCGGTATTAGTAGCGATGGGCATGGAACTGGAATTACATCAGTATC

     13030      13040      13050      13060      13070      13080
GTGGTCGCGTTAATCTAACCACCCAAATTGAAGACAGCTTATTACAGCAAGGTATTAACC

     13090      13100      13110      13120      13130      13140
TGACTGTTGAGCAACGTGAAGAACTGACCAATATTGCTAAAGACGGTGTTGCCTCGGCTG

     13150      13160      13170      13180      13190      13200
CACAGCTAAATCAGTATACGAGTTTCATTGGTAATATTATGGCGTCACGTATTTCGGCGT

     13210      13220      13230      13240      13250      13260
TATGGGATTTTTCTGGTCCTGCTATTACCGTATCGGCTGAAGAAAACTCTGTTTATCGTT

     13270      13280      13290      13300      13310      13320
GTGTTGAATTAGCTGAAAATCTATTTCAAACCAGTGATGTTGAAGCCGTTATTATTGCTG

     13330      13340      13350      13360      13370      13380
CTGTTGATTTGTCTGGTTCAATTGAAAACATTACTTTACGTCAGCACTACGGTCCAGTTA

     13390      13400      13410      13420      13430      13440
ATGAAAAGGGATCTGTAAGTGAATGTGGTCCGGTTAATGAAAGCAGTTCAGTAACCAACA

     13450      13460      13470      13480      13490      13500
ATATTCTTGATCAGCAACAATGGCTGGTGGGTGAAGGCGCAGCGGCTATTGTCGTTAAAC

     13510      13520      13530      13540      13550      13560
CGTCATCGCAAGTCACTGCTGAGCAAGTTTATGCGCGTATTGATGCGGTGAGTTTTGCCC

     13570      13580      13590      13600      13610      13620
CTGGTAGCAATGCGAAAGCAATTACGATTGCAGCGGATAAAGCATTAACACTTGCTGGTA

     13630      13640      13650      13660      13670      13680
TCAGTGCTGCTGATGTAGCTAGTGTTGAAGCACATGCAAGTGGTTTTAGTGCCGAAAATA
```

Fig. 6

```
      13690      13700      13710      13720      13730      13740
ATGCTGAAAAAACCGCGTTACCGACTTTATACCCAAGCGCAAGTATCAGTTCGGTGAAAG

      13750      13760      13770      13780      13790      13800
CCAATATTGGTCATACGTTTAATGCCTCGGGTATGGCGAGTATTATTAAAACGGCGCTGC

      13810      13820      13830      13840      13850      13860
TGTTAGATCAGAATACGAGTCAAGATCAGAAAAGCAAACATATTGCTATTAACGGTCTAG

      13870      13880      13890      13900      13910      13920
GTCGTGATAACAGCTGCGCGCATCTTATCTTATCGAGTTCAGCGCAAGCGCATCAAGTTG

      13930      13940      13950      13960      13970      13980
CACCAGCGCCTGTATCTGGTATGGCCAAGCAACGCCCACAGTTAGTTAAAACCATCAAAC

      13990      14000      14010      14020      14030      14040
TCGGTGGTCAGTTAATTAGCAACGCGATTGTTAACAGTGCGAGTTCATCTTTACACGCTA

      14050      14060      14070      14080      14090      14100
TTAAAGCGCAGTTTGCCGGTAAGCACTTAAACAAAGTTAACCAGCCAGTGATGATGGATA

      14110      14120      14130      14140      14150      14160
ACCTGAAGCCCCAAGGTATTAGCGCTCATGCAACCAATGAGTATGTGGTGACTGGAGCTG

      14170      14180      14190      14200      14210      14220
CTAACACTCAAGCTTCTAACATTCAAGCATCTCATGTTCAAGCGTCAAGTCATGCACAAG

      14230      14240      14250      14260      14270      14280
AGATAGCACCAAACCAAGTTCAAAATATGCAAGCTACAGCAGCCGCTGTAAGTTCACCCC

      14290      14300      14310      14320      14330      14340
TTTCTCAACATCAACACACAGCGCAGCCCGTAGCGGCACCGAGCGTTGTTGGAGTGACTG

      14350      14360      14370      14380      14390      14400
TGAAACATAAAGCAAGTAACCAAATTCATCAGCAAGCGTCTACGCATAAAGCATTTTTAG

      14410      14420      14430      14440      14450      14460
AAAGTCGTTTAGCTGCACAGAAAAACCTATCGCAACTTGTTGAATTGCAAACCAAGCTGT

      14470      14480      14490      14500      14510      14520
CAATCCAAACTGGTAGTGACAATACATCTAACAATACTGCGTCAACAAGCAATACAGTGC

      14530      14540      14550      14560      14570      14580
TAACAAATCCTGTATCAGCAACGCCATTAACACTTGTGTCTAATGCGCCTGTAGTAGCGA

      14590      14600      14610      14620      14630      14640
CAAACCTAACCAGTACAGAAGCAAAAGCGCAAGCAGCTGCTACACAAGCTGGTTTTCAGA

      14650      14660      14670      14680      14690      14700
TAAAAGGACCTGTTGGTTACAACTATCCACCGCTGCAGTTAATTGAACGTTATAATAAAC

      14710      14720      14730      14740      14750      14760
CAGAAAACGTGATTTACGATCAAGCTGATTTGGTTGAATTCGCTGAAGGTGATATTGGTA

      14770      14780      14790      14800      14810      14820
AGGTATTTGGTGCTGAATACAATATTATTGATGGCTATTCGCGTCGTGTACGTCTGCCAA
```

Fig. 6

```
     14830      14840      14850      14860      14870      14880
CCTCAGATTACTTGTTAGTAACACGTGTTACTGAACTTGATGCCAAGGTGCATGAATACA

     14890      14900      14910      14920      14930      14940
AGAAATCATACATGTGTACTGAATATGATGTGCCTGTTGATGCACCGTTCTTAATTGATG

     14950      14960      14970      14980      14990      15000
GTCAGATCCCTTGGTCTGTTGCCGTCGAATCAGGCCAGTGTGATTTGATGTTGATTTCAT

     15010      15020      15030      15040      15050      15060
ATATCGGTATTGATTTCCAAGCGAAAGGCGAACGTGTTTACCGTTTACTTGATTGTGAAT

     15070      15080      15090      15100      15110      15120
TAACTTTCCTTGAAGAGATGGCTTTTGGTGGCGATACTTTACGTTACGAGATCCACATTG

     15130      15140      15150      15160      15170      15180
ATTCGTATGCACGTAACGGCGAGCAATTATTATTCTTCTTCCATTACGATTGTTACGTAG

     15190      15200      15210      15220      15230      15240
GGGATAAGAAGGTACTTATCATGCGTAATGGTTGTGCTGGTTTCTTTACTGACGAAGAAC

     15250      15260      15270      15280      15290      15300
TTTCTGATGGTAAAGGCGTTATTCATAACGACAAAGACAAAGCTGAGTTTAGCAATGCTG

     15310      15320      15330      15340      15350      15360
TTAAATCATCATTCACGCCGTTATTACAACATAACCGTGGTCAATACGATTATAACGACA

     15370      15380      15390      15400      15410      15420
TGATGAAGTTGGTTAATGGTGATGTTGCCAGTTGTTTTGGTCCGCAATATGATCAAGGTG

     15430      15440      15450      15460      15470      15480
GCCGTAATCCATCATTGAAATTCTCGTCTGAGAAGTTCTTGATGATTGAACGTATTACCA

     15490      15500      15510      15520      15530      15540
AGATAGACCCAACCGGTGGTCATTGGGGACTAGGCCTGTTAGAAGGTCAGAAAGATTTAG

     15550      15560      15570      15580      15590      15600
ACCCTGAGCATTGGTATTTCCCTTGTCACTTTAAAGGTGATCAAGTAATGGCTGGTTCGT

     15610      15620      15630      15640      15650      15660
TGATGTCGGAAGGTTGTGGCCAAATGGCGATGTTCTTCATGCTGTCTCTTGGTATGCATA

     15670      15680      15690      15700      15710      15720
CCAATGTGAACAACGCTCGTTTCCAACCACTACCAGGTGAATCACAAACGGTACGTTGTC

     15730      15740      15750      15760      15770      15780
GTGGGCAAGTACTGCCACAGCGCAATACCTTAACTTACCGTATGGAAGTTACTGCGATGG

     15790      15800      15810      15820      15830      15840
GTATGCATCCACAGCCATTCATGAAAGCTAATATTGATATTTTGCTTGACGGTAAAGTGG

     15850      15860      15870      15880      15890      15900
TTGTTGATTTCAAAAACTTGAGCGTGATGATCAGCGAACAAGATGAGCATTCAGATTACC

     15910      15920      15930      15940      15950      15960
CTGTAACACTGCCGAGTAATGTGGCGCTTAAAGCGATTACTGCACCTGTTGCGTCAGTAG
```

Fig. 6

```
     15970      15980      15990      16000      16010      16020
CACCAGCATCTTCACCCGCTAACAGCGCGGATCTAGACGAACGTGGTGTTGAACCGTTTA

     16030      16040      16050      16060      16070      16080
AGTTTCCTGAACGTCCGTTAATGCGTGTTGAGTCAGACTTGTCTGCACCGAAAAGCAAAG

     16090      16100      16110      16120      16130      16140
GTGTGACACCGATTAAGCATTTTGAAGCGCCTGCTGTTGCTGGTCATCATAGAGTGCCTA

     16150      16160      16170      16180      16190      16200
ACCAAGCACCGTTTACACCTTGGCATATGTTTGAGTTTGCGACGGGTAATATTTCTAACT

     16210      16220      16230      16240      16250      16260
GTTTCGGTCCTGATTTTGATGTTTATGAAGGTCGTATTCCACCTCGTACACCTTGTGGCG

     16270      16280      16290      16300      16310      16320
ATTTACAAGTTGTTACTCAGGTTGTAGAAGTGCAGGGCGAACGTCTTGATCTTAAAAATC

     16330      16340      16350      16360      16370      16380
CATCAAGCTGTGTAGCTGAATACTATGTACCGGAAGACGCTTGGTACTTTACTAAAAACA

     16390      16400      16410      16420      16430      16440
GCCATGAAAACTGGATGCCTTATTCATTAATCATGGAAATTGCATTGCAACCAAATGGCT

     16450      16460      16470      16480      16490      16500
TTATTTCTGGTTACATGGGCACGACGCTTAAATACCCTGAAAAAGATCTGTTCTTCCGTA

     16510      16520      16530      16540      16550      16560
ACCTTGATGGTAGCGGCACGTTATTAAAGCAGATTGATTTACGCGGCAAGACCATTGTGA

     16570      16580      16590      16600      16610      16620
ATAAATCAGTCTTGGTTAGTACGGCTATTGCTGGTGGCGCGATTATTCAAAGTTTCACGT

     16630      16640      16650      16660      16670      16680
TTGATATGTCTGTAGATGGCGAGCTATTTTATACTGGTAAAGCTGTATTTGGTTACTTTA

     16690      16700      16710      16720      16730      16740
GTGGTGAATCACTGACTAACCAACTGGGCATTGATAACGGTAAAACGACTAATGCGTGGT

     16750      16760      16770      16780      16790      16800
TTGTTGATAACAATACCCCCGCAGCGAATATTGATGTGTTTGATTTAACTAATCAGTCAT

     16810      16820      16830      16840      16850      16860
TGGCTCTGTATAAAGCGCCTGTGGATAAACCGCATTATAAATTGGCTGGTGGTCAGATGA

     16870      16880      16890      16900      16910      16920
ACTTTATCGATACAGTGTCAGTGGTTGAAGGCGGTGGTAAAGCGGGCGTGGCTTATGTTT

     16930      16940      16950      16960      16970      16980
ATGGCGAACGTACGATTGATGCTGATGATTGGTTCTTCCGTTATCACTTCCACCAAGATC

     16990      17000      17010      17020      17030      17040
CGGTGATGCCAGGTTCATTAGGTGTTGAAGCTATTATTGAGTTGATGCAGACCTATGCGC

     17050      17060      17070      17080      17090      17100
TTAAAAATGATTTGGGTGGCAAGTTTGCTAACCCACGTTTCATTGCGCCGATGACGCAAG
```

Fig. 6

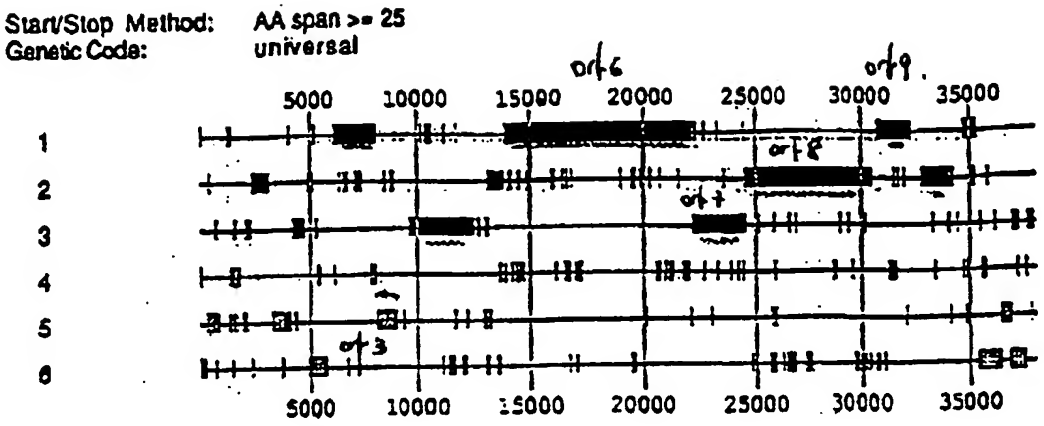
```
     17110      17120      17130      17140      17150      17160
TTGATTGGAAATACCGTGGGCAAATTACGCCGCTGAATAAACAGATGTCACTGGACGTGC

     17170      17180      17190      17200      17210      17220
ATATCACTGAGATCGTGAATGACGCTGGTGAAGTGCGAATCGTTGGTGATGCGAATCTGT

     17230      17240      17250      17260      17270      17280
CTAAAGATGGTCTGCGTATTTATGAAGTTAAAAACATCGTTTTAAGTATTGTTGAAGCGT

     17290      17300      17310      17320      17330      17340
AAAGGGTCAAGTGTAACGTGCTTAAGCGCCGCATTGGTTAAAGACGCTTTGCACGCCGTG

     17350      17360      17370      17380      17390      17400
AATCCGTCCATGGAGGCTTGGGGTTGGCATCCATGCCAACAACAGCAAGCTTACTTTAAT

     17410      17420      17430      17440      17450      17460
CAATACGGCTTGGTGTCCATTTAGACGCCTCGAACTTAGTAGTTAATAGACAAAATAATT

     17470      17480      17490      17500      17510      17520
TAGCTGTGGAATGAATATAGTAAGTAATCATTCGGCAGCTACAAAAAAGGAATTAAGAAT

     17530      17540      17550      17560      17570      17580
GTCGAGTTTAGGTTTTAACAATAACAACGCAATTAACTGGGCTTGGAAAGTAGATCCAGC

     17590      17600      17610      17620      17630      17640
GTCAGTTCATACACAAGATGCAGAAATTAAAGCAGCTTTAATGGATCTAACTAAACCTCT

     17650      17660      17670      17680      17690      17700
CTATGTGGCGAATAATTCAGGCGTAACTGGTATAGCTAATCATACGTCAGTAGCAGGTGC

     17710      17720      17730      17740      17750      17760
GATCAGCAATAACATCGATGTTGATGTATTGGCGTTTGCGCAAAAGTTAAACCCAGAAGA

     17770      17780      17790      17800      17810      17820
TCTGGGTGATGATGCTTACAAGAAACAGCACGGCGTTAAATATGCTTATCATGGCGGTGC

     17830      17840      17850      17860      17870      17880
GATGGCAAATGGTATTGCCTCGGTTGAATTGGTTGTTGCGTTAGGTAAAGCAGGGCTGTT

     17890      17900      17910      17920      17930      17940
ATGTTCATTTGGTGCTGCAGGTCTAGTGCCTGATGCGGTTGAAGATGCAATTCGTCGTAT

     17950      17960      17970      17980      17990      18000
TCAAGCTGAATTACCAAATGGCCCTTATGCGGTTAACTTGATCCATGCACCAGCAGAAGA

     18010      18020      18030      18040      18050      18060
AGCATTAGAGCGTGGCGCGGTTGAACGTTTCCTAAAACTTGGCGTCAAGACGGTAGAGGC

     18070      18080      18090      18100      18110      18120
TTCAGCTTACCTTGGTTTAACTGAACACATTGTTTGGTATCGTGCTGCTGGTCTAACTAA

     18130      18140      18150      18160      18170      18180
AAACGCAGATGGCAGTGTTAATATCGGTAACAAGGTTATCGCTAAAGTATCGCGTACCGA

     18190      18200      18210      18220      18230      18240
AGTTGGTCGCCGCTTTATGGAACCTGCACCGCAAAAATTACTGGATAAGTTATTAGAACA
```

Fig. 6

```
     18250      18260      18270      18280      18290      18300
AAATAAGATCACCCCTGAACAAGCTGCTTTAGCGTTGCTTGTACCTATGGCTGATGATAT

     18310      18320      18330      18340      18350      18360
TACTGGGGAAGCGGATTCTGGTGGTCATACAGATAACCGTCCGTTTTTAACATTATTACC

     18370      18380      18390      18400      18410      18420
GACGATTATTGGTCTGCGTGATGAAGTGCAAGCGAAGTATAACTTCTCTCCTGCATTACG

     18430      18440      18450      18460      18470      18480
TGTTGGTGCTGGTGGTGGTATCGGAACGCCTGAAGCAGCACTCGCTGCATTTAACATGGG

     18490      18500      18510      18520      18530      18540
CGCGGCTTATATCGTTCTGGGTTCTGTGAATCAGGCGTGTGTTGAAGCGGGTGCATCTGA

     18550      18560      18570      18580      18590      18600
ATATACTCGTAAACTGTTATCGACAGTTGAAATGGCTGATGTGACTATGGCACCTGCTGC

     18610      18620      18630      18640      18650      18660
AGATATGTTTGAAATGGGTGTGAAGCTGCAAGTATTAAAACGCGGTTCTATGTTCGCGAT

     18670      18680      18690      18700      18710      18720
GCGTGCGAAGAAACTGTATGACTTGTATGTGGCTTATGACTCGATTGAAGATATCCCAGC

     18730      18740      18750      18760      18770      18780
TGCTGAACGTGAGAAGATTGAAAAACAAATCTTCCGTGCAAACCTAGACGAGATTTGGGA

     18790      18800      18810      18820      18830      18840
TGGCACTATCGCTTTCTTTACTGAACGCGATCCAGAAATGCTAGCCCGTGCAACGAGTAG

     18850      18860      18870      18880      18890      18900
TCCTAAACGTAAAATGGCACTTATCTTCCGTTGGTATCTTGGCCTTTCTTCACGCTGGTC

     18910      18920      18930      18940      18950      18960
AAACACAGGCGAGAAGGGACGTGAAATGGATTATCAGATTTGGGCAGGCCCAAGTTTAGG

     18970      18980      18990      19000      19010      19020
TGCATTCAACAGCTGGGTGAAAGGTTCTTACCTTGAAGACTATACCCGCCGTGGCGCTGT

     19030      19040      19050      19060      19070      19080
AGATGTTGCTTTGCATATGCTTAAAGGTGCTGCGTATTTACAACGTGTAAACCAGTTGAA

     19090      19100      19110      19120      19130      19140
ATTGCAAGGTGTTAGCTTAAGTACAGAATTGGCAAGTTATCGTACGAGTGATTAATGTTA

     19150      19160      19170      19180      19190      19200
CTTGATGATATGTGAATTAATTAAAGCGCCTGAGGGCGCTTTTTTTGGTTTTTAACTCAG

     19210      19220
GTGTTGTAACTCGAAATTGCCCCTTTC
```

Fig. 6

A


Start/Stop Method: AA span >= 25
Genetic Code: universal
orf6
orf9
orf8
orf7
orf3
1
2
3
4
5
6
5000
10000
15000
20000
25000
30000
35000

B

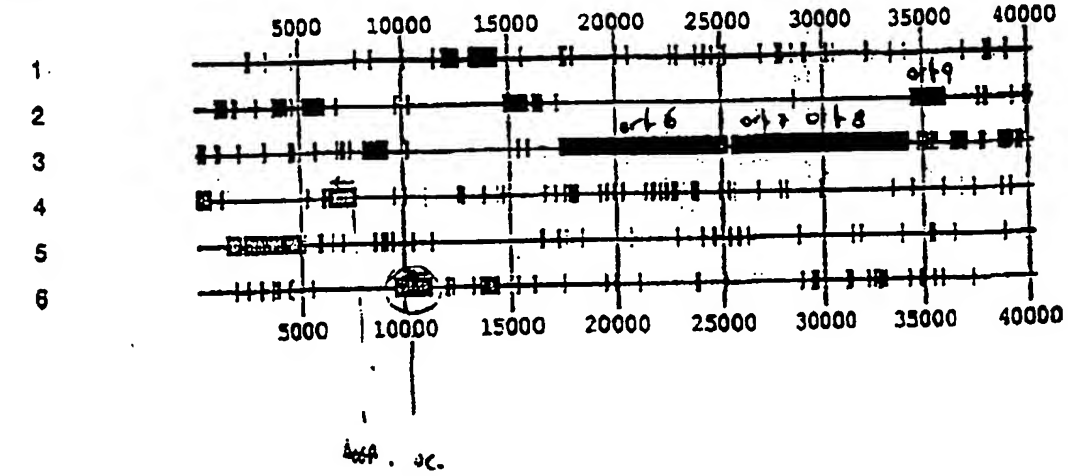

Start/Stop Method: AA span >= 25
Genetic Code: universal
orf9
orf6
orf7 orf8
1
2
3
4
5
6
5000
10000
15000
20000
25000
30000
35000
40000

FIG 7

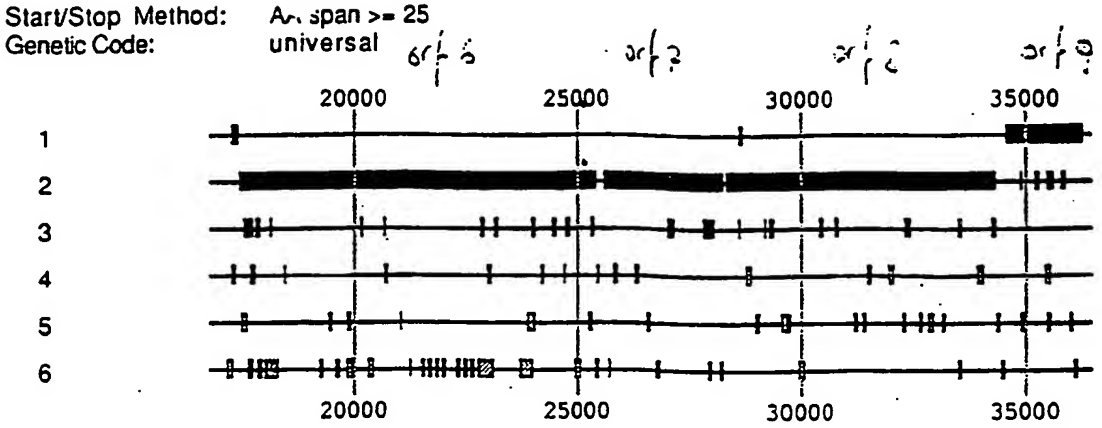

Start/Stop Method: A.. span >= 25
Genetic Code: universal
orf 5
orf 3
orf 2
orf 1
20000
25000
30000
35000
1
2
3
4
5
6
20000
25000
30000
35000

Fig. 8

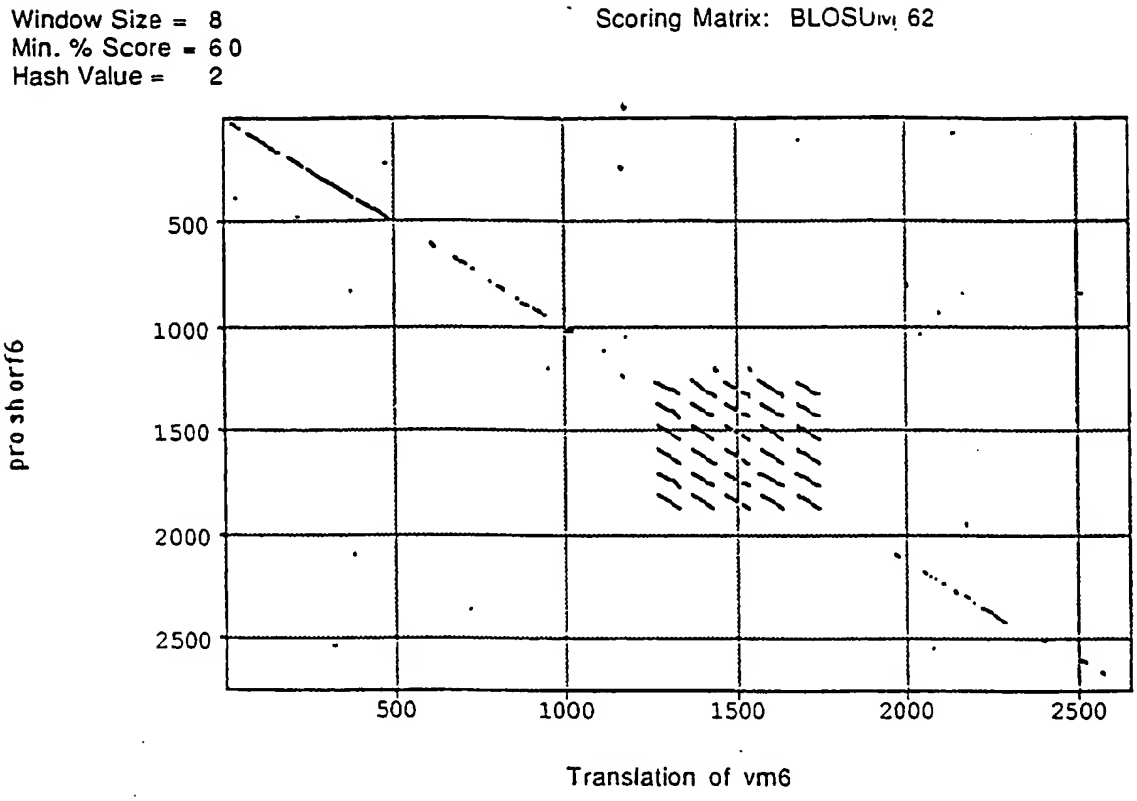

Window Size = 8
Min. % Score = 60
Hash Value = 2
Scoring Matrix: BLOSUM 62
pro sh orf6
500
1000
1500
2000
2500
Translation of vm6

Fig. 9

Window Size = 8
Min. % Score = 60
Hash Value = 2

Scoring Matrix: BLOSUM 62

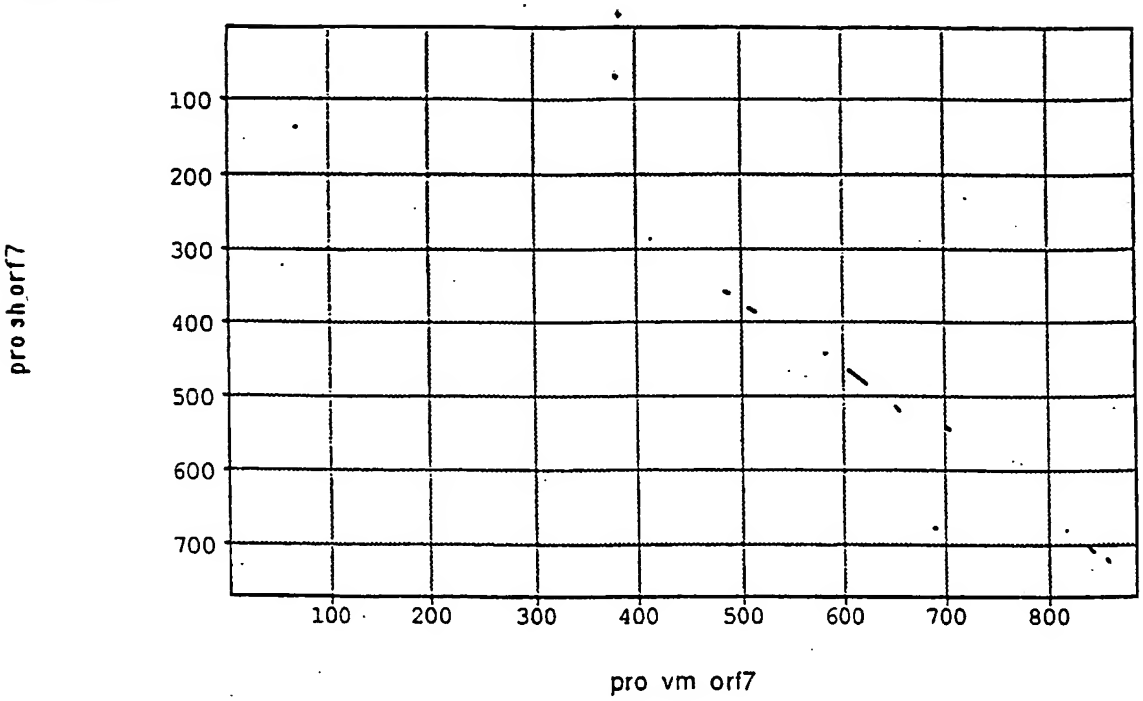


Fig. 10

Window Size = 8
Min. % Score = 6 0
Hash Value = 2

Scoring Matrix: BLOS 62

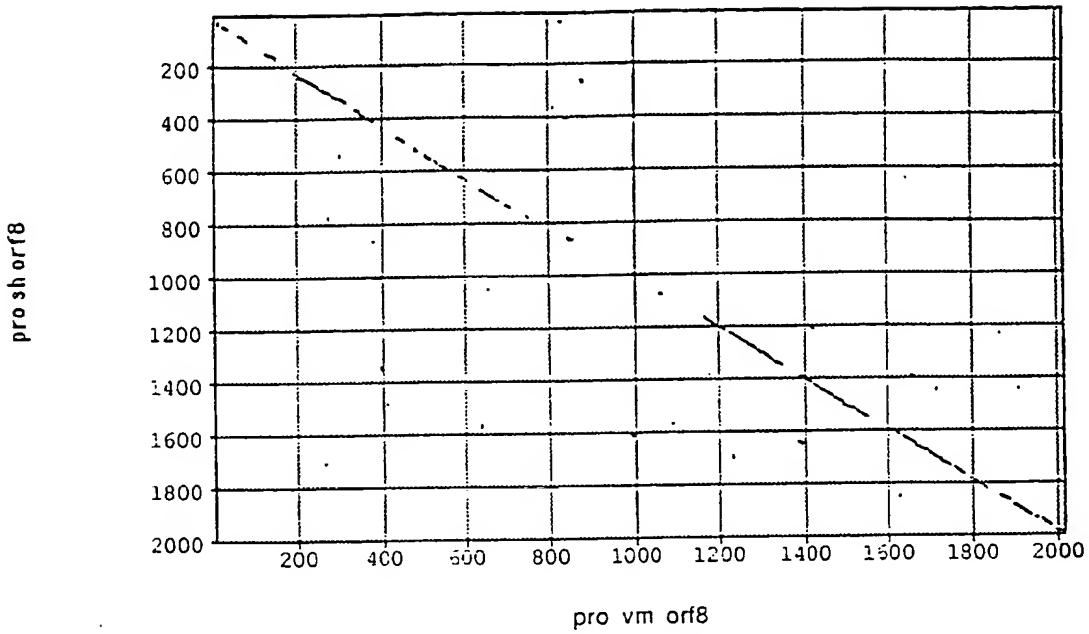


Fig. 11

Window Size = 8
Min. % Score = 60
Hash Value = 2

Scoring Matrix: BLOS . 62

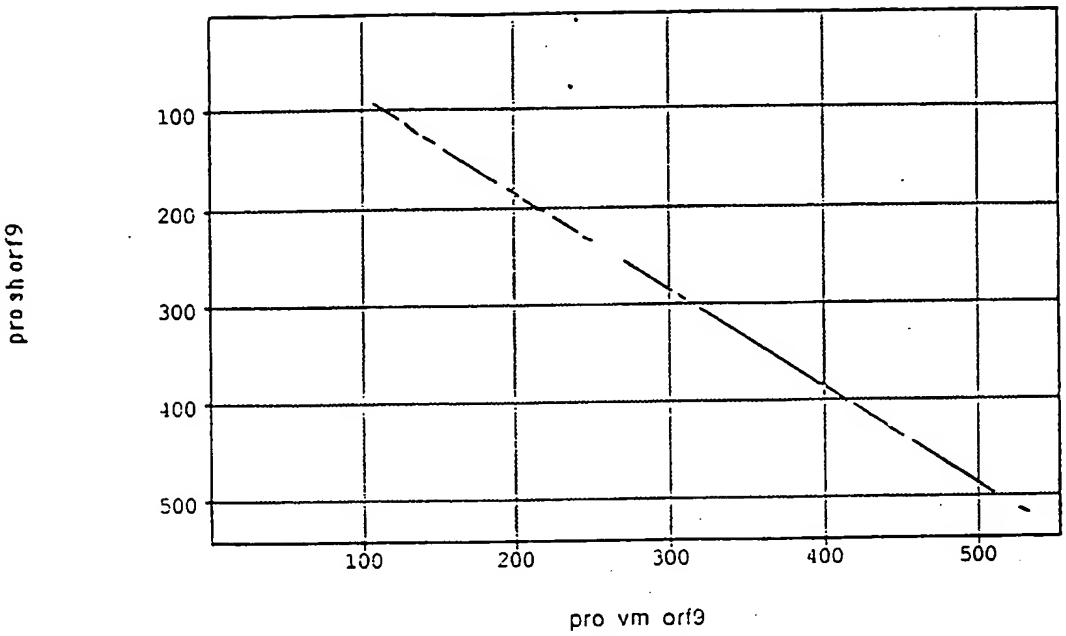


Fig. 12

CO' 'LEMENTATION Sp / Vm

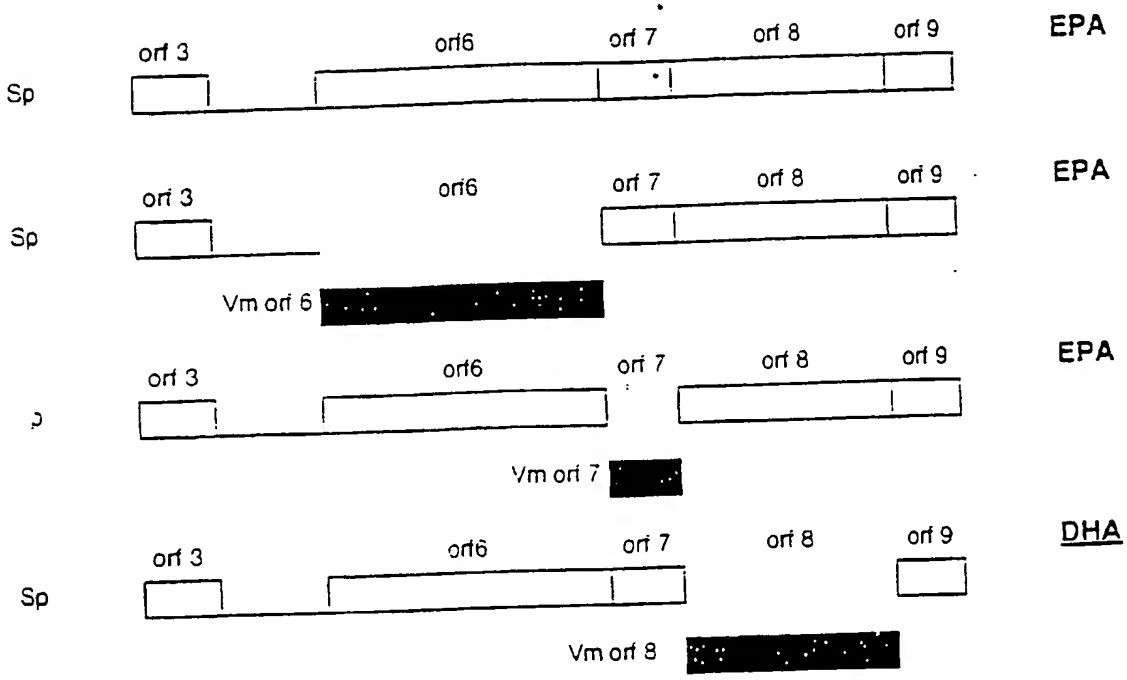


Fig. 13

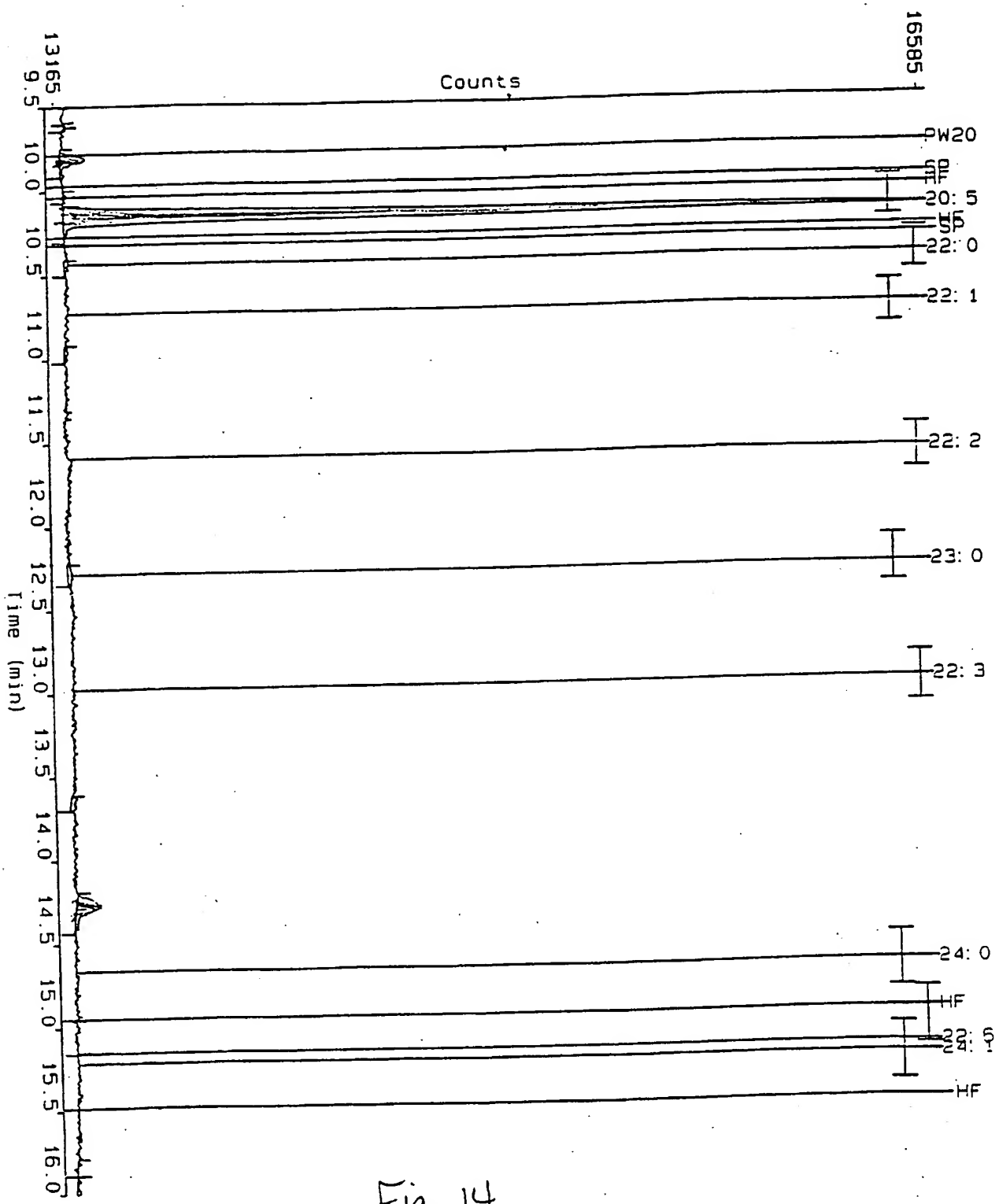

16585
13165
Counts
9.5
10.0
10.5
11.0
11.5
12.0
12.5
13.0
13.5
14.0
14.5
15.0
15.5
16.0
Time (min)
PW20
20: 5
22: 0
22: 1
22: 2
23: 0
22: 3
24: 0
HF
HF

Fig. 14

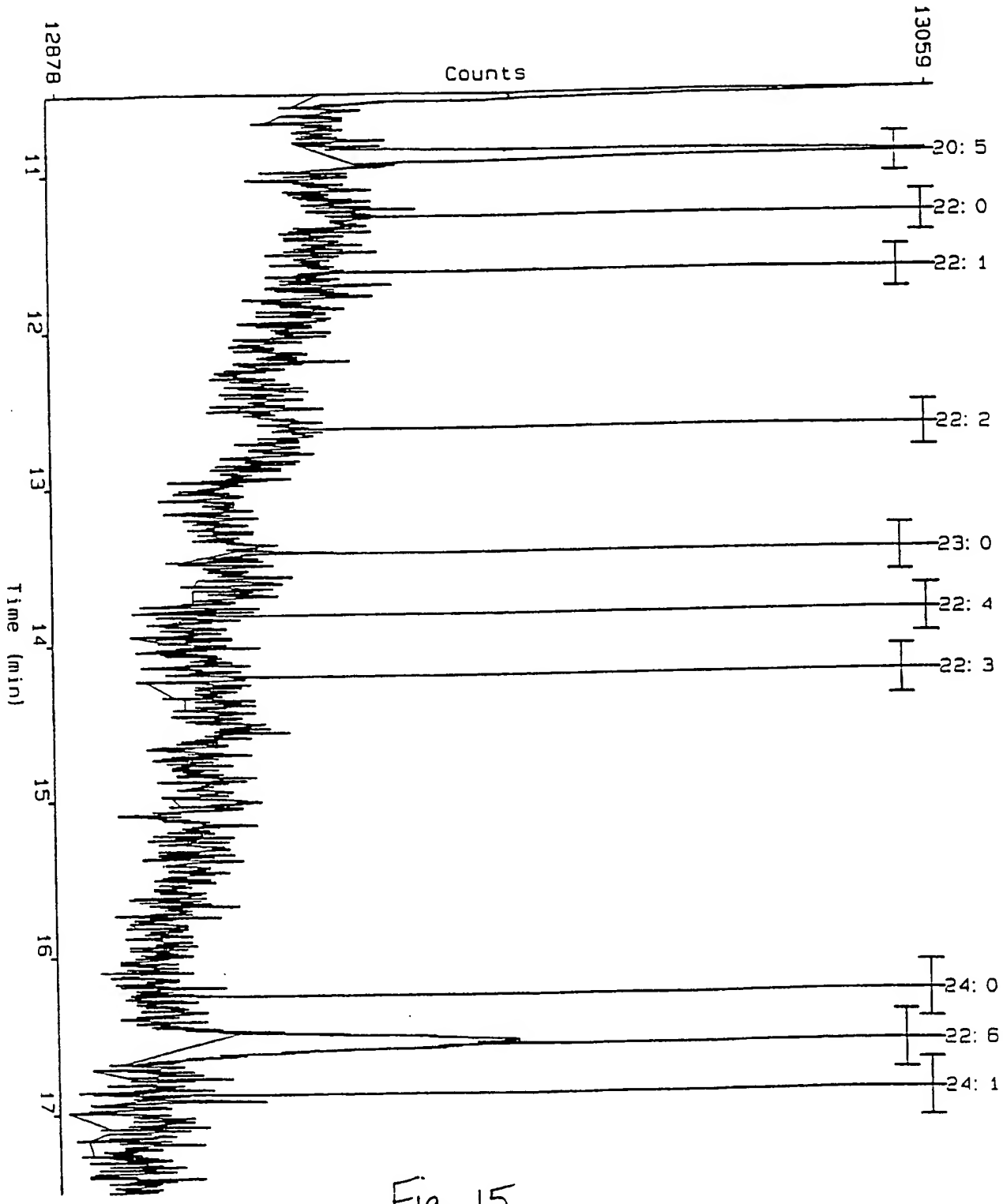

12878
Counts
13059
11
12
13
14
15
16
17
Time (min)
20: 5
22: 0
22: 1
22: 2
23: 0
22: 4
22: 3
24: 0
22: 6
24: 1

Fig. 15

EPA (% Fatty acids)	DHA (% Fatty acids)	20°C
0.00	0.06	pEPAD8
0.60	0.70	4
0.64	0.66	5
0.33	0.22	6s
0.45	0.59	6l
		23°C
0.02	0.06	pEPAD8
0.32	0.62	4
0.27	0.22	6s
0.18	0.65	6l

Fig. 16

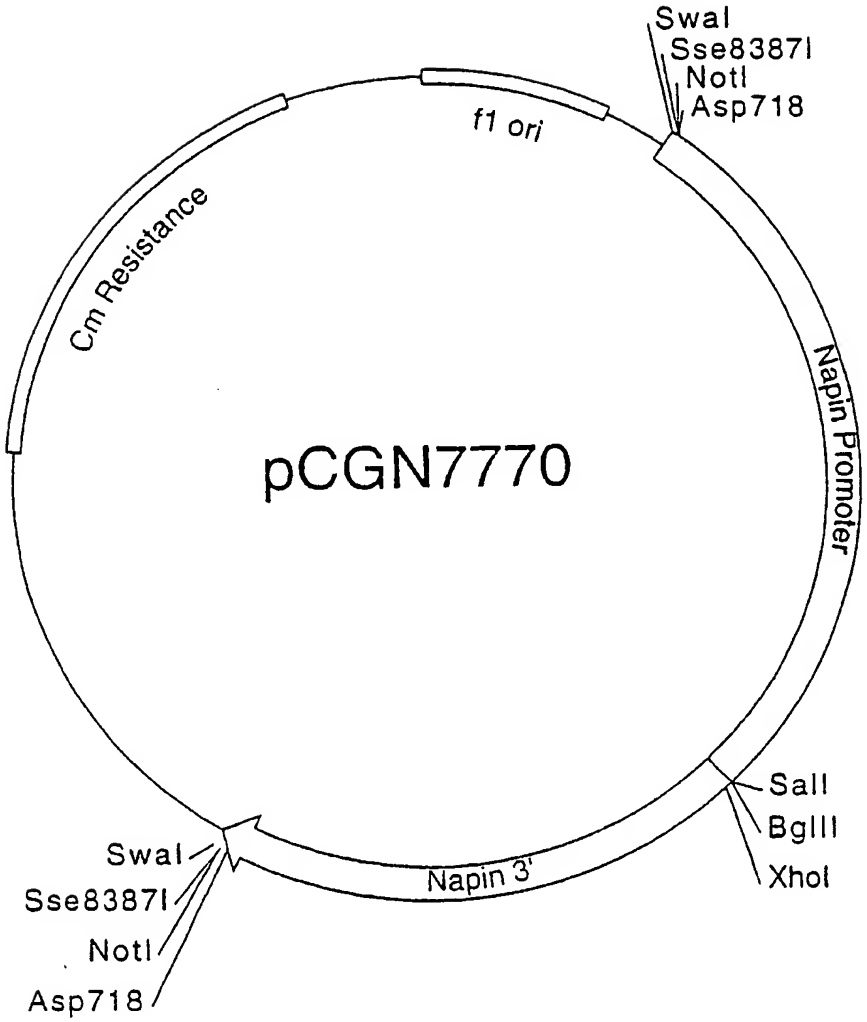

SwaI
Sse8387I
NotI
Asp718
f1 ori
Cm Resistance
Napin Promoter
pCGN7770
SalI
BglII
XhoI
Napin 3'
SwaI
Sse8387I
NotI
Asp718

FIG 17

pCGN8537

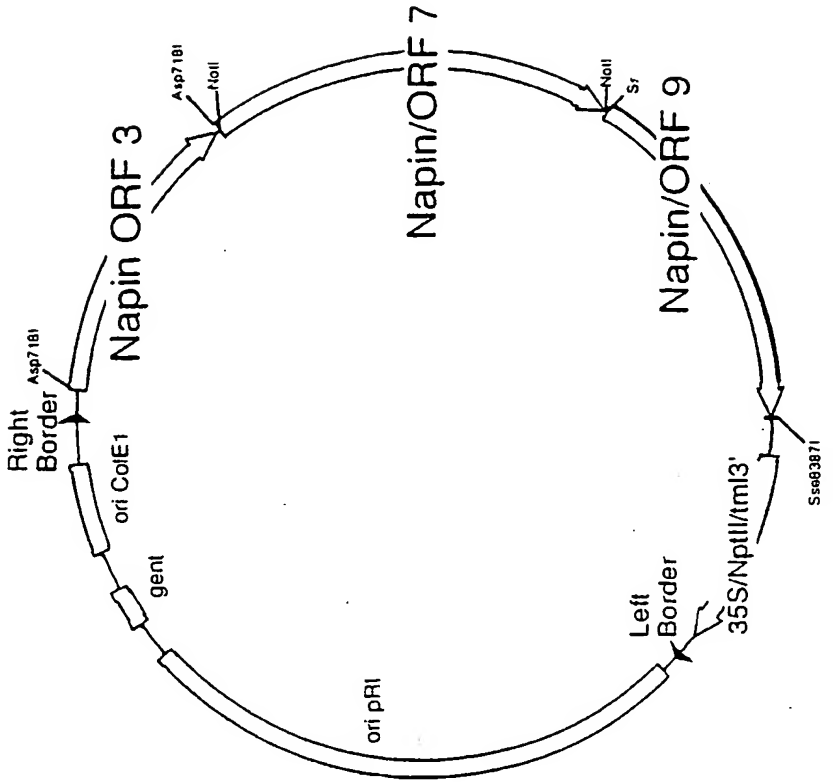


FIG 19

pCGN8535

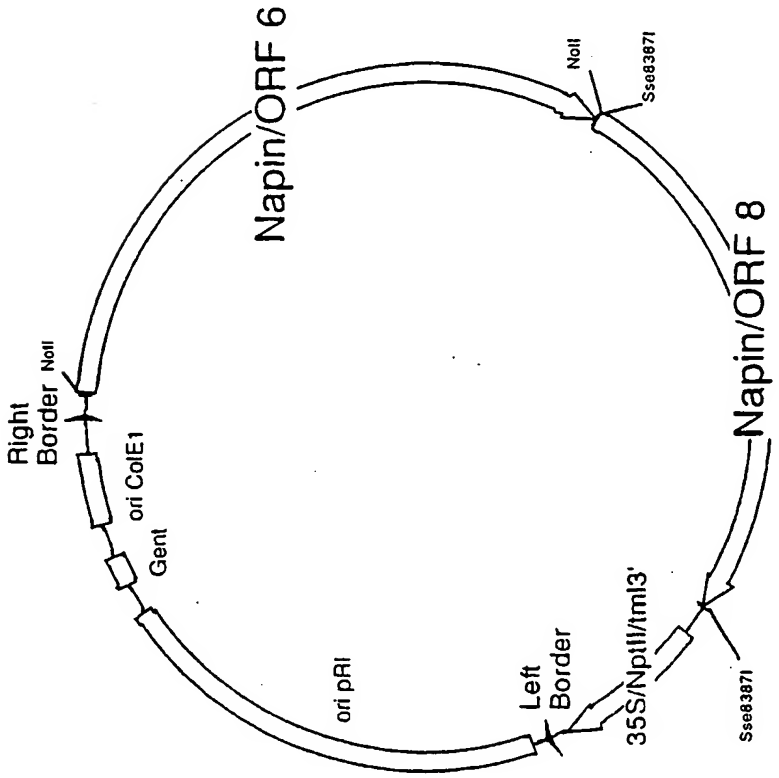


FIG 18

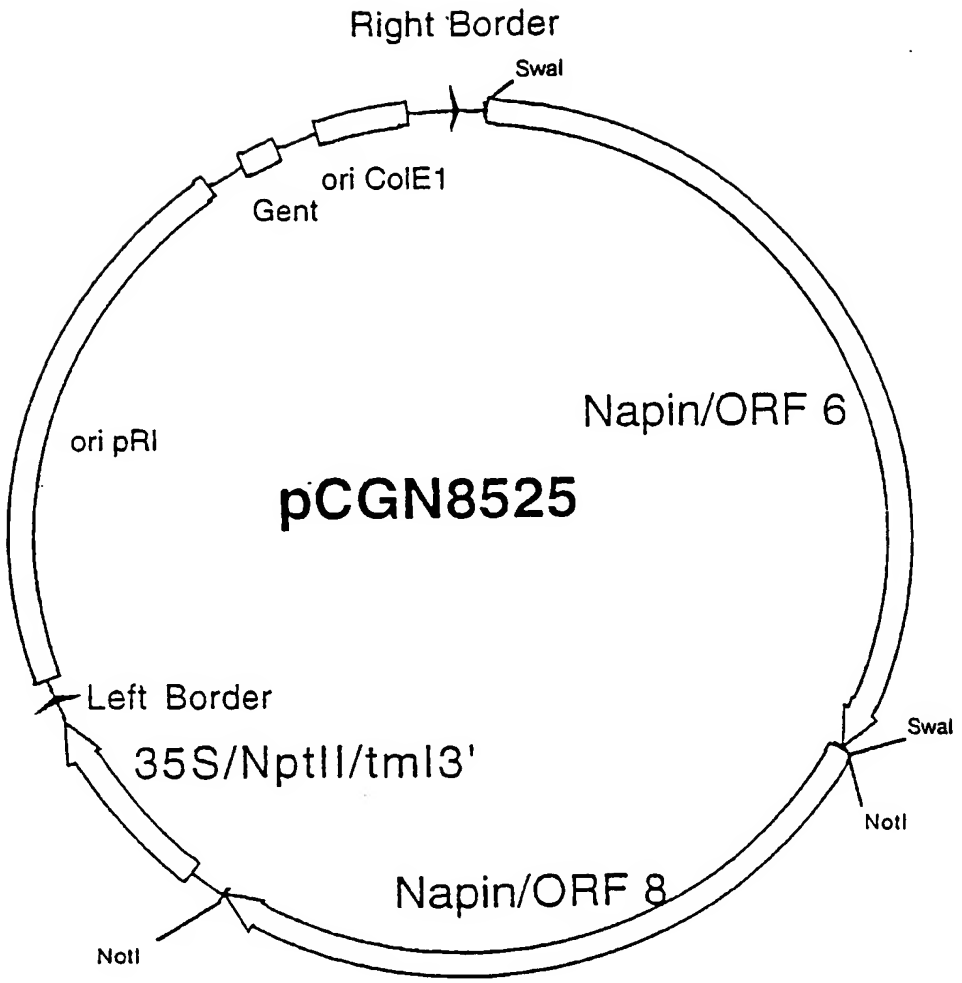

Right Border
SwaI
ori ColE1
Gent
Napin/ORF 6
ori pRI
pCGN8525
Left Border
35S/NptII/tml3'
SwaI
NotI
Napin/ORF 8
NotI

FIG 20

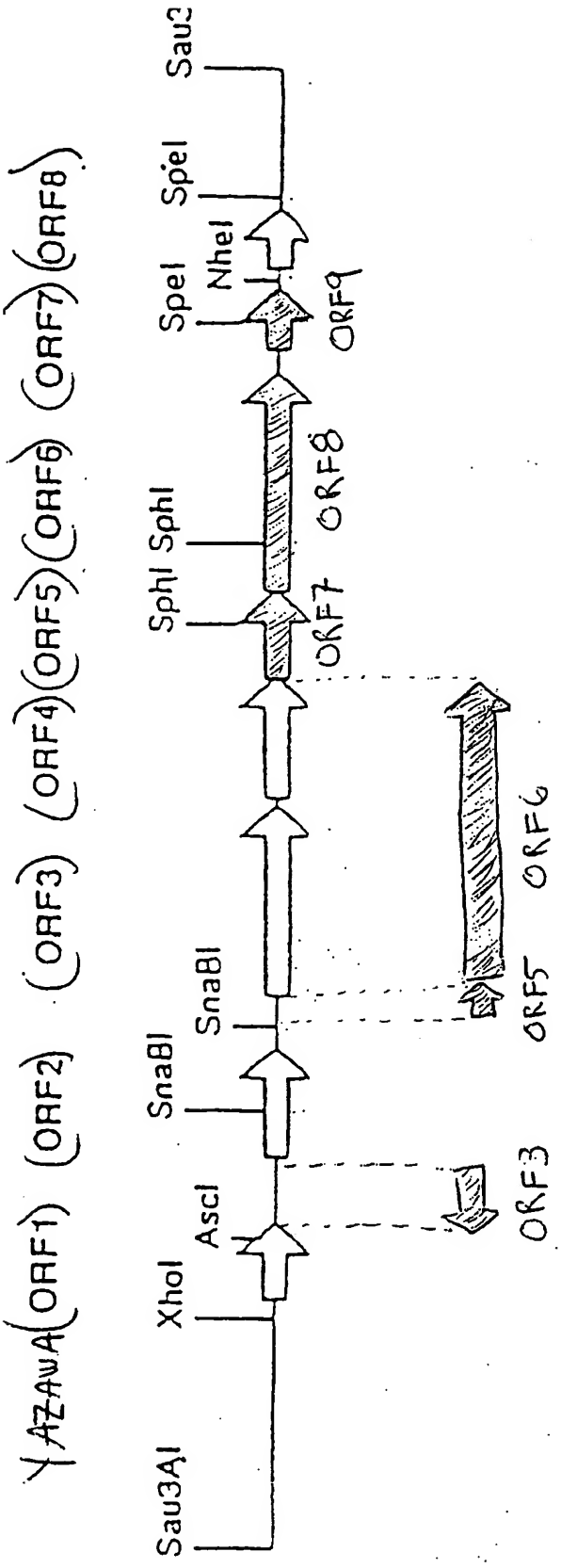

YAZAWA(ORF1) (ORF2) (ORF3) (ORF4)(ORF5)(ORF6) (ORF7)(ORF8)
Sau3AI
XhoI
AscI
SnaBI
SnaBI
SphI SphI
SpeI
NheI
SpeI
Sau3
ORF3
ORF5
ORF6
ORF7
ORF8
ORF9

FIG 21

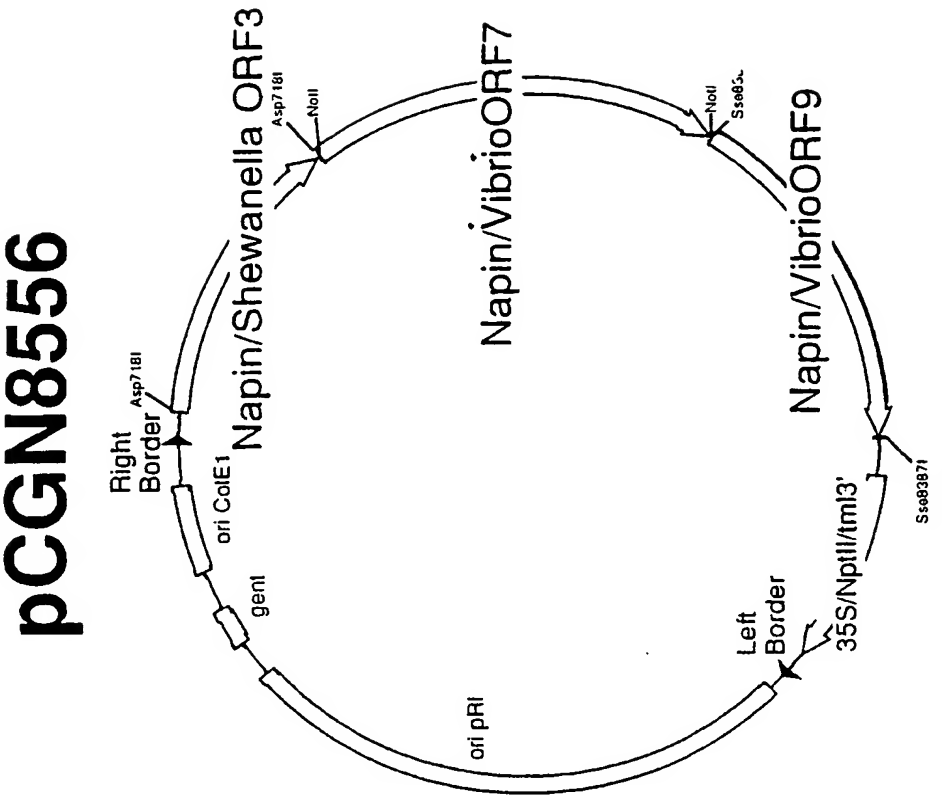

pCGN8556
Napin/Shewanella ORF3
Napin/VibrioORF7
Napin/VibrioORF9
Right Border
Asp718I
ori ColE1
genI
ori pRI
Left Border
35S/NptII/tml3'
Sse8387I
NotI

FIG 23

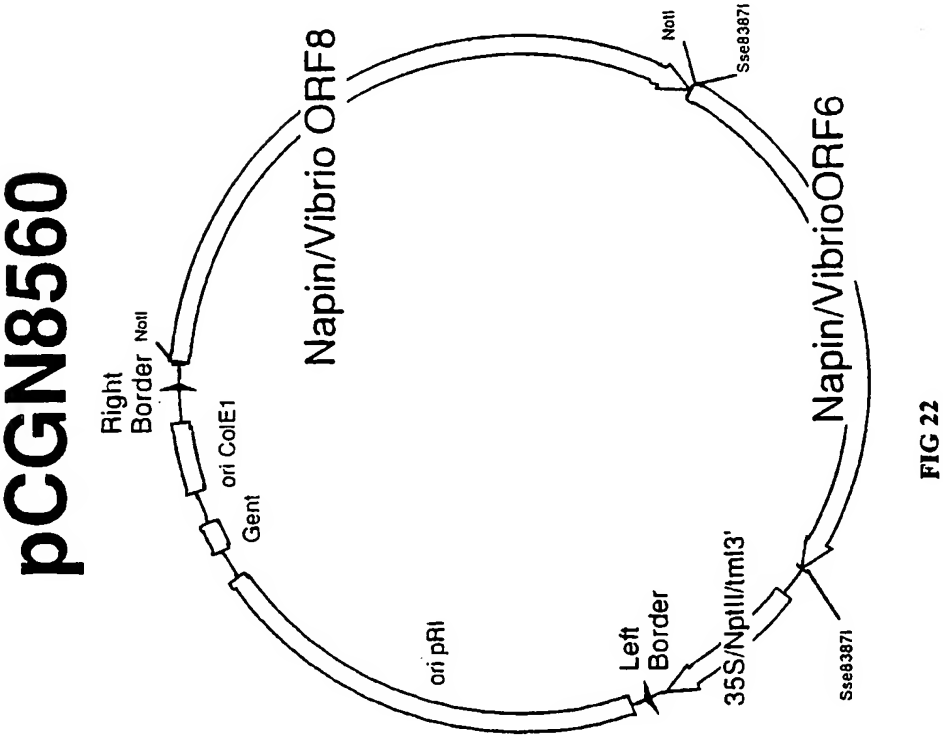

pCGN8560
Napin/Vibrio ORF8
Napin/VibrioORF6
Right Border
NotI
ori ColE1
Gent
ori pRI
Left Border
35S/NptII/tml3'
Sse8387I

FIG 22

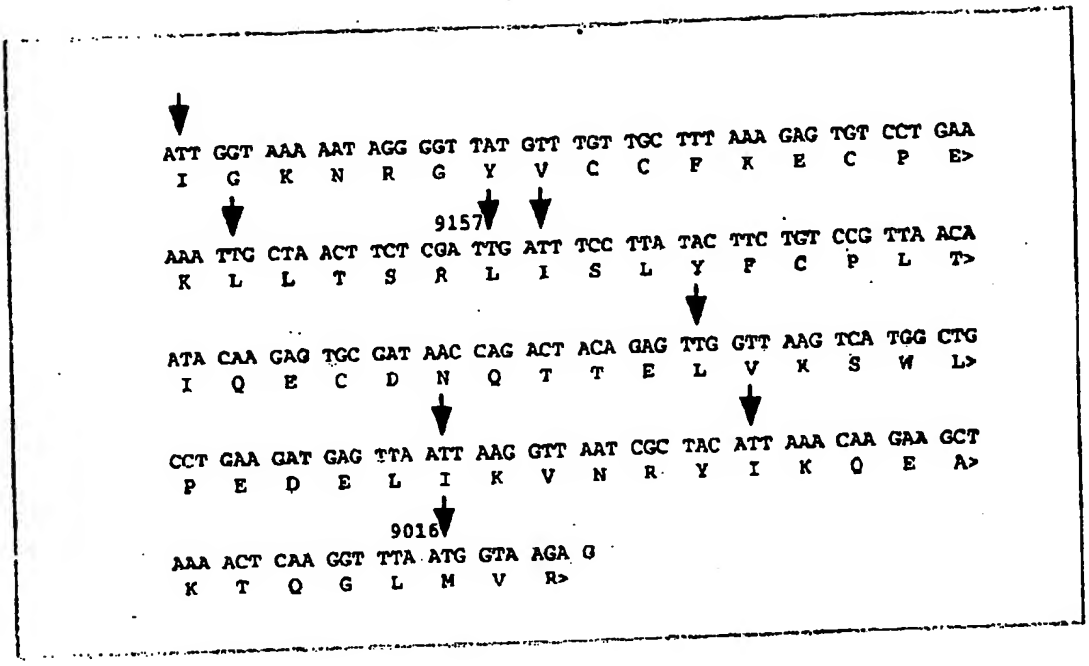

ATT GGT AAA AAT AGG GGT TAT GTT TGT TGC TTT AAA GAG TGT CCT GAA
I G K N R G Y V C C F K E C P E>
9157
AAA TTG CTA ACT TCT CGA TTG ATT TCC TTA TAC TTC TGT CCG TTA ACA
K L L T S R L I S L Y F C P L T>
ATA CAA GAG TGC GAT AAC CAG ACT ACA GAG TTG GTT AAG TCA TGG CTG
I Q E C D N Q T T E L V K S W L>
CCT GAA GAT GAG TTA ATT AAG GTT AAT CGC TAC ATT AAA CAA GAA GCT
P E D E L I K V N R Y I K Q E A>
9016
AAA ACT CAA GGT TTA ATG GTA AGA G
K T Q G L M V R>

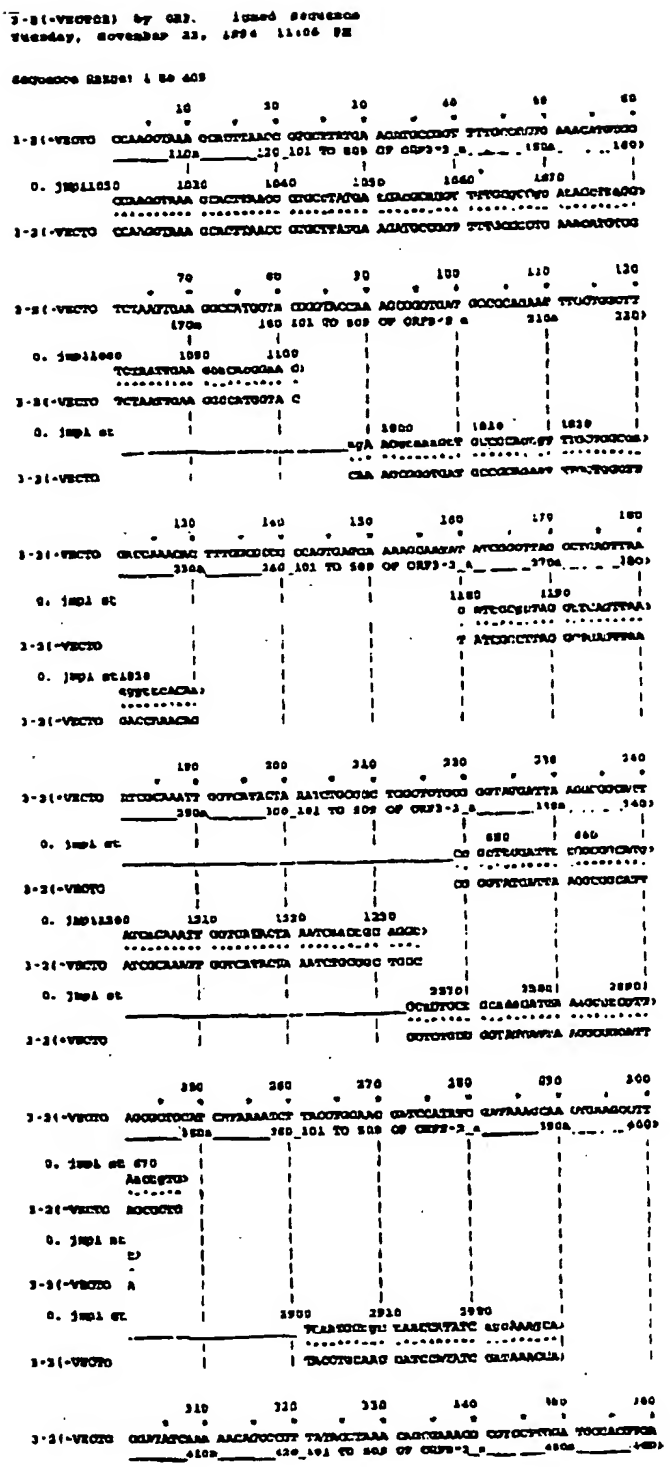
FIG 24

```
        10         20         30         40         50         60
AGCGAAATGCTTATCAAGAAATTCCAAGATCAATACATCACTGGGAAGAAAATTCATTCC

        70         80         90        100        110        120
CTGGTTCACTGGGTAACGTTATTTCCGGCCGTATTGCTAACCGCTTCGACCTTGGTGGCA

       130        140        150        160        170        180
TGAACTGTGTCGTTGATGCAGCATGTGCAGGCCCTCTTGCTGCATTGCGTATGGCATTAA

       190        200        210        220        230        240
GCGAGCTTGTTGAAGGCCGCAGCGAAATGATGATTACAGGTGGTGTGTGTACCGATAACT

       250        260        270        280        290        300
CACCAACCATGTACATGAGCTTCTCTAAAACACCGGCATTCACGACAAACGAAACAATTC

       310        320        330        340        350        360
AACCATTCGATATTGACTCGAAAGGTATGATGATTGGTGAAGGTATCGGTATGATTGCGC

       370        380        390        400        410        420
TTAAACGTCTTGAAGACGCAGAGCGTGATGGCGACCGTATCTATTCCGTGATTAAAGGTG

       430        440        450        460        470        480
TTGGGTGCATCTTCAGACGGTAATTTATTAAGAGTANTTATGCGCNTCGTCCTGAAGGTC

       490        500        510        520        530        540
AGGCTAAGGCACTTAAACGTGCTTACGACGATGCAGGTTTCGCACCGCACACACTTGGCT

       550        560        570        580        590        600
TACTTGAAGCCCACGGCACAGGCACAGCAGCAGGTGATGTGGCAGAATTCAGTGGTCTTA

       610        620        630        640        650        660
ACTCTGTATTCAGTGAAGGCAATGACGAAAAGCAACACATCGCATTAGGTTCAGTGAAAT

       670        680        690        700        710        720
CACAGATTGGTCACACTAAATCAACAGCGGGTACTGCGGGTCTAATCAAAGCGTCTTTAG

       730        740        750        760        770        780
CACTGCACCATAAAGTACTGCCGCCAACAATCAATGTAACCAGCCCTAACCCTAAACTGA

       790        800        810        820        830        840
ATATTGAAGACTCGCCTTTCTACCTCAATACACAGACGCGTCCATGGATGCAACGTGTCG

       850        860        870        880
ATGGTACACCGCGTCGTGCTGGTATTAGCTCATTTGGTTTTGGTG
```

SS9 Photobacter

PCR Product Using Primers
Presented in Example I

FIG 25



ORF 6
Probe Resulting from PCR with Primers Presented in Example I

FIG 26A

FIG 26B

INTERNATIONAL SEARCH REPORT

Int tional Application No
PC:/US 98/11639

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/31 C12N15/52 C12N15/82 C12N15/70 C12N5/10
C12N1/21 C12P7/64 A01H5/00

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C12P C07K A01H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NAKAHARA, TORO: "Physiological activity of docosahexaenoic acid (DHA) and its production by microbial culture" YUKAGAKU (1995), 44(10), 821-7 CODEN: YKGKAM;ISSN: 0513-398X, XP002080682	6,7, 11-13
A	see abstract	14,32

X	NASU M ET AL: "Efficient transformation of Marchantia polymorpha that is haploid and has very small genome DNA;Agrobacterium tumefaciens-mediated transformation of suspension cell culture, for use in eicosapentaenoic acid, arachidonic acid and antibiotic production" J.FERMENT.BIOENG.;(1997) 84, 6, 519-23 CODEN: JFBIEX ISSN: 0922-338X, XP002080470 see the whole document	25,27, 28,30

	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 October 1998	23/10/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kania, T

3

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/US 98/11639

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category ³	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	KYLE D ET AL: "Long-chain omega-3 polyunsaturated fatty acids: prospects for introduction into horticultural food plants; e.g. alga eicosapentaenoic acid and docosahexaenoic acid gene cloning, expression in transgenic plant oil, crop improvement (conference paper)" HORTSCIENCE;(1990) 25, 12, 1523-26 CODEN: HJHSAR, XP002080471 * see the whole document, esp. p.1524, 2nd par. *	25-28, 30,31
X	EP 0 594 868 A (SAGAMI CHEM RES) 4 May 1994 cited in the application see the whole document	15-17, 19-22,24
X	WO 96 21735 A (SAGAMI CHEM RES) 18 July 1996 cited in the application see the whole document	15-17, 19-22,24
A	YAZAWA, KAZUNAGA: "Production of eicosapentaenoic acid from marine bacteria" LIPIDS (1996), 31(SUPPL., FATTY ACIDS AND LIPIDS FROM CELL BIOLOGY TO HUMAN DISEASE), S297-S300 CODEN: LPDSAP;ISSN: 0024-4201, XP002080483 cited in the application see the whole document	1-32
A	SOMERVILLE C R: "Future prospects for genetic modification of the composition of edible oils from higher plants; oilseed crop improvement by lipid and fatty acid modification (conference paper)" AM.J.CLIN.NUTR.;(1993) 58, 2, SUPPL., 270S-275S CODEN: AJCNAC, XP002080472 * see esp. p.274S, r. col., 1st par. *	1-32

3

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ional Application No
PCT/US 98/11639

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0594868 A	04-05-1994	AU 673359 B	07-11-1996
		AU 4088193 A	13-12-1993
		CA 2113557 A	25-11-1993
		FI 940203 A	14-03-1994
		WO 9323545 A	25-11-1993
		JP 6046864 A	22-02-1994
		NO 940146 A	14-03-1994
		US 5683898 A	04-11-1997
		US 5798259 A	25-08-1998
WO 9621735 A	18-07-1996	AU 4400196 A	31-07-1996
		CA 2209987 A	18-07-1996
		EP 0831149 A	25-03-1998
		JP 8242867 A	24-09-1996

THIS PAGE BLANK (USPTO)